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Medical
Faxon

THE PROLONGATION OF PREGNANCY AND COMPLICATIONS OF PARTURITION IN THE RABBIT FOLLOWING INDUCTION OF OVULATION NEAR TERM

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Submitted for publication July 24, 1933

INTRODUCTION

Numerous observations have shown that in the rabbit ovulation can be induced at any stage of pregnancy by a single injection of extract of anterior lobe or urine of pregnant women. A fresh set of corpora lutea can be added to the ovaries as desired. In the present experiments, animals near term have been provided by this method with a fresh set of corpora lutea in an attempt to determine the rôle of corpora lutea in parturition.

Previous studies have demonstrated the far-reaching effects on pregnancy of the administration of anterior lobe or urine of pregnant women. Teel (1926) experimentally produced delay of implantation in rats by the daily injection of anterior lobe extract and noted prolongation of gestation which corresponded approximately to the period of delay of implantation. The fetuses reached maturity but invariably died in the uterus, being extruded within 48 hours after death. Engle and Mermod (1928) made daily implants of anterior lobe in rats and mice beginning at various stages of gestation. Interruption of pregnancy usually occurred although, in animals in which implants were begun during the last third of pregnancy, normal litters were frequently born at term. The writers suggested that interruption of pregnancy would occur with sufficiently large dosage. Ovulation was not observed while fetuses were alive but only after their death. Zondek and Aschheim (1928) emphasized the importance of dosage. After a single implant in a mouse, ova were seen in the tube which was obtained while the fetuses were alive. Evans and Simpson (1928) described impair-

ment of the birth mechanism in rats following implants of anterior lobe and administration of human urine and placental extracts. In the rabbit, ovulation during pregnancy was observed following implants or extracts of anterior lobe and urine of pregnant women (Courrier and Kehl (1930), Wolfe (1931), Snyder and Wislocki (1931), Hill and Parkes (1932)). Ovulation was followed frequently by interruption of pregnancy. The fate of the fetuses was studied in detail by Hill and Parkes.

From the preceding studies it was evident that even during pregnancy the administration of anterior lobe or extract of urine would result in a marked increase of lutein tissue in the ovaries. In the rabbit, conditions seemed especially favorable for determination of the influence of an increase in lutein tissue, since by a single injection a fresh growth of lutein cells may be induced which can be readily distinguished by their circumscribed distribution as a crop of ruptured follicles. The isolation of the newly added lutein tissue favored the attempt to correlate structural changes of the corpora lutea with the effects on pregnancy. The occurrence of ovulation about 10 hours after injection permitted accurate estimate of the time of onset of formation of the corpus luteum.

There was evidence also that the corpora lutea formed after ovulation induced with anterior lobe extract, were normal. In one of our animals, pregnancy followed induced ovulation. Since coitus had not occurred, artificial insemination was accomplished by introduction of spermatic fluid into the vagina from a pipette. A normal litter was born 32 days after the injection of anterior lobe extract.

In the present attempt, therefore, to observe the final stage of gestation in the presence of fresh corpora lutea at the phase of their maximal activity, it is obvious that the difficulty does not lie in experimentally increasing the amount of lutein tissue in the ovaries, but rather in obtaining such an increase without interruption of pregnancy.

METHODS AND MATERIALS

In the present study, firstly a method favorable for avoiding the interruption of pregnancy was investigated by modifying in turn dosage, stage of pregnancy at injection, and parity. Secondly, after adoption of a uniform procedure, elucidation of the mechanism of prolongation of pregnancy was undertaken. All of the experiments

have been recorded in the present paper, however, including the results in animals studied before standardization of a satisfactory method.

For the induction of ovulation during pregnancy Antuitrin S was used, which was prepared under the supervision of Dr. Oliver Kamm of Parke, Davis & Co. from the urine of pregnant women. Only 2 lots of extract of urine were required. To two-thirds of the entire series of animals extract no. 1 was given, while the remaining one-third of the animals, which were the last to be injected, received extract no. 2. The material was not kept out of the ice box longer than a few minutes. Extract no. 1 was used for a period of 61 days after arrival in the laboratory, and extract no. 2 was used within 37 days. Extract no. 1 contained 200 rat units per cubic centimeter, and extract no. 2 contained 100 rat units per cubic centimeter, according to the assay in Dr. Kamm's laboratory. The material also contained 0.5 per cent phenol as a preservative. Regarding the assay, a communication from Dr. Kamm was as follows: "One Rat Unit is the minimum quantity of hormone which will cause the formation of corpora lutea within 96 to 100 hours when injected subcutaneously in six doses, twice daily for 3 days, into female white rats 30 days of age and taken from a colony the members of which become sexually mature normally in 50 to 60 days. Age of the rats, food and other factors have great importance in quantitative determinations. Rats vary in susceptibility to the hormone, but an accurate result is obtained by using 10 rats for each dose and accepting, as the minimal effective dose, that on which at least 60 per cent of the rats are found to have developed corpora lutea. . . . . The preparation undergoes a certain amount of deterioration and usually at the end of the expiration date of 3 months, it is likely to be somewhat below 100 units" (*i.e.*, the initial potency). The minimal effective dose, according to Friedmann (1932), for the production of ovulation in a post-partum rabbit was about 1 rat unit per kilogram using extract of urine supplied and assayed on rats by Parke, Davis & Co.

The present observations were based on a series of 59 pregnancies in 46 different rabbits. Extract of urine was injected intravenously during a single pregnancy in 33 animals, while in 13 animals the experiment was repeated in a subsequent pregnancy. Successive pregnancies in the same animal were indicated by number, *e.g.*, 30-1, 30-2.

The total number of pregnancies of a given animal were noted in the tables, including the one which was being studied experimentally. No animals were omitted from the series, which represents a complete consecutive record. The rabbits were of known age, ranging from 6 to 12 months, and were in the laboratory from the time of maturity. In animals of this stock which were observed during normal pregnancy, the gestation period was found to average about 32 days, just as noted by Hammond (p. 179).

OBSERVATIONS ON PROLONGED PREGNANCY

In the present observations on a series of 57 animals injected about the 25th day of gestation with extract of urine, it was found that the termination of pregnancy was altered in every animal. The outstanding change from normal pregnancy in these animals was failure of parturition to occur at term, *i.e.*, on the 32nd day. Normal expulsion of a litter of mature living fetuses on the 32nd day was not observed in the entire series.

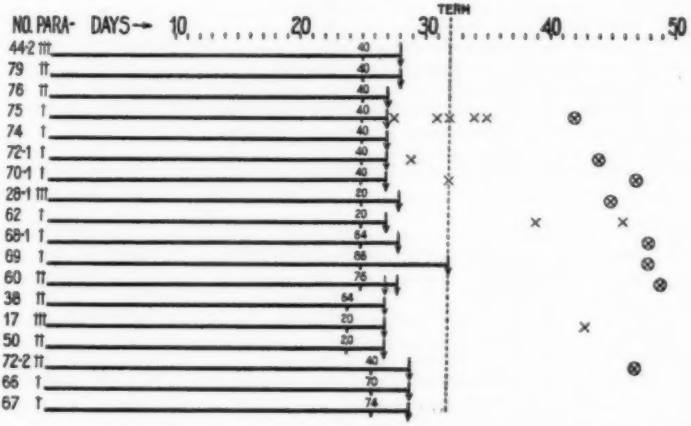
Instead of normal parturition, pregnancy was terminated either by abortion, or was prolonged beyond term. In the entire series of 57 animals, abortion of the whole litter occurred in 18 cases (table 1), while prolongation of pregnancy beyond term occurred in 39 instances, or more than twice as often as complete abortion (table 2). Among the group of 39 cases of prolonged pregnancy there were 13 animals in which abortion of part of the litter occurred, although the rest of the litter remained alive and were not cast out until long past term.

Despite this marked alteration in the termination of pregnancy, it was found that the onset of parturition was not totally irregular but tended to occur at a definite time. When pregnancy was prolonged beyond term, the onset of parturition was most frequently about 15 days following injection, *i.e.*, on the 40th day of pregnancy. Among the total 39 animals in which pregnancy was prolonged, the onset of parturition occurred 38 to 42 days after mating in 19 cases; later than 42 days in 11 cases, and earlier than 38 days in 2 cases. Of 7 remaining cases, hysterotomy was done earlier than 38 days on 4 animals, and a second injection of urine extract was given to 3 animals.

When pregnancy terminated in abortion, the fetuses were cast out on the 2nd or 3rd day following injection, but not on the first day. This

was true in 17 of the 18 cases in which there was abortion of the entire litter, as well as in 12 of 13 other animals in which only part of the litter was aborted, while other members of the litter survived in the uterus and were carried beyond term. In an exceptional case, no. 69, 4 macerated fetuses were expelled on the 32nd day. Death of the litter had occurred about 7 days previously, *i.e.*, at the time of injection, as

TABLE 1

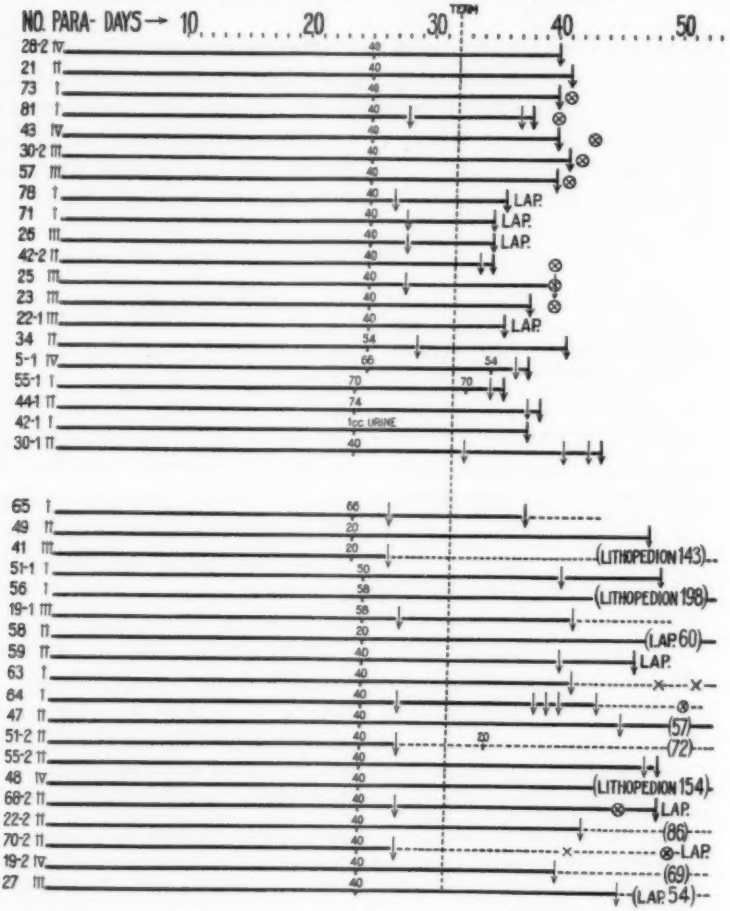


In the total series of 57 animals, abortion of the entire litter occurred in 18 cases. This table summarizes the pertinent data of each case, including the time of injection of the urine extract, the dosage expressed in rat units per kilogram, and the time of complete emptying of the uterus. It will be noted that abortion was never observed within 24 hours after injection, but was limited to the second or third day (except No. 69), and occurred predominantly in primiparae. Evidence of the altered functional state of the ovaries is indicated by the absence of ovulation after coitus (designated by X) until at least the 39th day, i.e., a week past term. Coitus followed by ovulation is shown by X with a circle.

indicated by the stage of development of the embryos. In 7 cases in which pregnancy was prolonged beyond term, one or two macerated, immature fetuses were expelled at the time of extrusion of the postmature fetuses. Retention of these immature fetuses was related apparently to the survival of postmature fetuses implanted nearer to the cervical end of the uterine horn, so that escape of the immature fetuses was obstructed.

TABLE 2

Prolonged pregnancies following injection of extract of urine of pregnant women



In the entire series of 57 animals, there was prolongation of pregnancy in 39 cases. Each case is summarized in the table, giving the time of injection, the dosage expressed in rat units per kilogram, and the number of days parturition was delayed past term. Complete emptying of the uterus is indicated by heavy arrows; extrusion of part of a litter by light arrows. In the second half of the table are grouped the cases in which fetuses were retained for prolonged periods, often exceeding the number of days which could be represented on the chart. In such instances the number of days of retention is shown in parenthesis. Complete emptying of the uterus never occurred in some cases, although the animals still survived. Evidence of the functional state of the ovaries with regard to ovulation is indicated by the occurrence of ovulation after coitus (designated by X with a circle) and by the absence of ovulation after coitus, marked by X alone.

The termination of pregnancy was markedly altered not only as to the time of onset of parturition but also with respect to the duration of the period during which fetuses were expelled. In about half of the cases of prolonged pregnancy many days elapsed between the onset of expulsion of postmature fetuses and the completion of emptying of the uterus. In fact, parturition was never completed in at least 7 animals. The fetuses were retained in the uterus as a stony mass for an indefinitely prolonged period. In table 2, the animals were divided for convenience into 2 groups. In the first group of 20 animals, spontaneous termination of pregnancy occurred usually about the end of the life span of the corpora lutea; in the remaining group of 19 animals, complete emptying of the uterus was delayed for indefinitely prolonged intervals. On the other hand, in the 18 animals in which abortion of the entire litter occurred, the fetuses were usually expelled within a few hours, and the interval rarely extended beyond a single day.

Before considering at further length the changes in parturition which have been outlined it is important to take into account variations in the method of the experiment. At the beginning of the present experiments it became of interest to note any factors which might be favorable to the prolongation of pregnancy rather than termination in abortion. It appeared that such factors might include the stage of pregnancy at injection, the amount of extract of urine injected, and the primiparous or multiparous state of the animal. Accordingly, injections were made in one group of animals on the 24th, in another on the 25th, and in a third group on the 26th day of pregnancy. The dosage was varied from 20 rat units per kilo to 86. Primiparous animals were used as well as rabbits which had borne 1, 2 or 3 litters previously.

To summarize the results briefly, it was found that a reliable method for the experimental production of prolonged pregnancy by means of inhibition of parturition at term was available by the administration of a single intravenous injection of 40 rat units per kilogram of extract of urine of pregnant women (Antuitrin "S," Parke, Davis & Co.) into multiparous rabbits 25 days after mating. By this procedure in a series of 23 animals, pregnancy was prolonged in 20 of them, or 87 per cent.

Factors influencing the prolongation of pregnancy

Concerning the number of animals observed under varying conditions with regard to the stage of pregnancy at injection, dosage, multiparity, and the relative importance of these factors in determining the time of termination of pregnancy, the following data were obtained.

In the entire series of 57 pregnancies it was found that prolongation of gestation occurred in 32 of the 44 animals injected on the 25th day, and in 7 of the 10 animals injected on the 24th day, or about 73 and 70 per cent, respectively. In the 3 remaining animals injected on the 26th day, there was abortion of the entire litter in every case. Abortion of part of the litter in animals with prolonged pregnancy injected on the 25th day, occurred in 11 of the 32 cases, while it was noted in 2 of the 7 cases of prolonged gestation in animals injected on the 24th day.

With regard to the amount of extract of urine injected, it was found that pregnancy was prolonged in 27 of the 35 animals injected with 40 rat units per kilogram, in 8 of the 14 animals injected with 50 to 80 units per kilogram, and in 3 of 7 animals injected with 20 units per kilogram, or 77, 57 and 43 per cent, respectively. Of animals with prolonged gestation, abortion of part of the litter occurred in 9 of the 27 animals injected with 40 rat units per kilogram, in 3 of 8 animals injected with 50 to 80 rat units per kilogram, and in 1 of 3 animals injected wth 20 rat units per kilogram.

In the entire series of 57 animals, there were 37 multiparae and 20 primiparae. Of the 37 multiparae, pregnancy was prolonged in 28 cases, while of the 20 primiparae prolonged pregnancy occurred in 11 cases, or 75 and 55 per cent, respectively. Abortion of part of the litter occurred in 8 of the 28 multiparae with prolonged gestation and in 5 of the 11 primiparae.

The foregoing outline of results in the entire series may be more accurately evaluated by consideration of a group of 33 animals in which both the stage of pregnancy at injection and the dosage were kept constant. In this group of 33 cases from the total series of 57 animals, injection was made on the 25th day in every case, and each animal received 40 units per kilogram. Among the 33 animals, there were 23 multiparae and 10 primiparae. It was found that prolongation of pregnancy occurred in 20 of the 23 multiparae, or 87 per cent,

while it occurred in only 6 of 10 primiparae, or 60 per cent. There was abortion of the entire litter in the remaining animals, *i.e.*, in 3 of 23 multiparae, or 13 per cent, as compared to 4 of the 10 primiparae, or 40 per cent. Abortion of part of the litter of the animals with prolonged pregnancy was likewise less than half as frequent in multiparae, being noted in 5 of the 20 multiparous animals, or 25 per cent, while it was seen in 4 of the 6 primiparae, or 66 per cent.

In a group of 11 animals injected on the 25th day but in which the dosage was altered, there was prolonged pregnancy in 6 cases, or 55 per cent, while abortion of the entire litter occurred in 5 cases, or 45 per cent. Thus, in 8 animals which received an increased dosage of 50 to 80 rat units of urine extract per kilogram, pregnancy was prolonged in 5 cases, of which 2 were primiparae, while in the remaining 3 cases there was abortion of the entire litter, 2 of the animals being primiparae. In 3 other animals the dosage was decreased to 20 units per kilogram. Two of the animals aborted their entire litter, one being a primipara, while in one animal (a multipara) pregnancy was prolonged.

In a group of 8 animals injected on the 24th day with a dosage increased to 50 to 80 units per kilogram in half of the cases, and decreased to 20 units in half, there was prolonged pregnancy in 5 animals, or 62 per cent. In the 4 animals injected with 50 to 80 units per kilogram, pregnancy was prolonged in 3, of which 2 were primiparae, while the remaining animal, a multipara, aborted. In the 4 animals injected with 20 units per kilogram, pregnancy was prolonged in 2, both multiparae, and abortion occurred in 2, also multiparae.

Two additional animals were injected on the 24th day and pregnancy was prolonged without abortion of any fetuses. One, a primipara no. 42-1, received a total dose of 3 cc. of untreated urine obtained from a pregnant woman at term. The other animal, no. 30-1, a multipara, received 40 rat units per kilogram of extract of urine.

Injection on the 26th day in 3 animals was followed by abortion of the entire litter. One animal was a multipara which received 40 units per kilogram, while 2 were primiparae which received 70 and 74 units per kilogram, respectively.

In addition to the 57 cases described above there were 2 additional animals observed in the total series of 59 consecutive pregnancies.

Both were injected on the 25th day with 40 rat units per kilogram. In the first animal (no. 77) hysterotomy on the 32nd day showed a living fetus. A fresh set of corpora lutea was in the ovaries and except for interference evidently pregnancy would have been prolonged. In the second case (no. 5) death occurred following injection, the fetuses being retained in the uterus.

Fate of the fetuses

In view of the theories regarding the relation of changes in the fetus to the onset of parturition, the fate of the fetuses under the conditions of the experiments was of unusual interest. In the entire series, it was noted that in event of abortion the fetuses were not macerated as a rule, but corresponded in size and weight to the day of pregnancy at which expulsion occurred. In fact, in 5 cases the fetuses were still alive when found. In 12 of the 18 cases in which abortion of the entire litter occurred, the fetuses showed no maceration and were of normal external appearance. In 4 cases there was excoriation of the skin and signs of maceration. In 2 cases the fetuses were devoured except fragments. Of the 13 animals with prolonged pregnancy in which abortion of part of the litter occurred, the fetuses likewise were not macerated, and corresponded in development to the day of expulsion. Vaginal bleeding was associated with the abortion, and frequently was profuse.

When parturition failed to occur at term and pregnancy was prolonged, it was found that the fetuses survived and continued to grow. Development progressed until the fetuses resembled newborn rabbits 3 days after birth. While still in the uterus the fetal body was covered with a conspicuous growth of hair and there was a corresponding increase in size and weight (fig. 1). The fetuses attained a crown-rump length of 125 mm. in contrast to an average at term of about 100 mm., while the weight was about 80 gm. instead of an average at term of about 55 gm. This marked growth was characteristic of litters numbering 8 to 14 fetuses (nos. 51, 25, 26, 30-2, 43, etc.) as well as litters of 1 to 3 fetuses (nos. 71, 59, 81). In the maternal animals with large litters of postmature fetuses the abdominal walls bulged conspicuously and locomotion was awkward. For instance, in no. 23 the litter numbered 14 and weighed 1000 grams at birth on

the 38th day, or about one-fourth of the post-partum weight of the mother.

FIG. 1. POSTMATURE FETUS FROM LITTER OF EIGHT, BORN ON THE 38TH DAY (NO. 5-1), AND NORMAL NEWBORN, 32ND DAY

Regarding the rate of growth, evidence was available in animals in which abortion of part of the litter occurred about the 28th day, while the rest of the litter survived in the uterus. Comparison of the immature fetuses, born about the 28th day, with the rest of the litter

born postmaturely showed that there was an increase in weight from about 30 grams at 28 days to about 80 grams at 35 days, while the crown-rump length increased from 75 mm. in these immature to 125 mm. in the postmature fetuses of the same litter. During this period the surface of the body acquired a thick covering of hair.

Direct evidence of the survival of fetuses in the uterus for at least 3 days past term was obtained by hysterotomy and removal of living fetuses 35 days after mating (nos. 26, 71). In no. 26, there were 12 fetuses in the uterus, but only one remained alive, and died soon after removal. In no. 71, the single fetus was alive, and survived in the laboratory. In 2 animals examined on the 36th day, the fetuses were not alive (nos. 78, 22-1). The litters were small, consisting of 2 fetuses in no. 78 and 4 fetuses in no. 22-1. The fetuses removed on the 35th and 36th day corresponded in size, weight and external appearance with the average development of fetuses of the entire series in which pregnancy was prolonged. Death of the fetuses was not due to detachment of the placentae from the uterine wall. After removal of the dead fetuses by hysterotomy in nos. 26, 78, 22-1, the placentae were separated manually, hemorrhage occurring at the site of detachment.

The excessive size which the fetuses may attain in prolonged pregnancy was strikingly illustrated in no. 59, which died after prolonged labor with a fetus still in the uterus. The animal, which had had one previous pregnancy, was injected with urine extract on the 25th day after mating. Abdominal palpation showed increase in size of the fetuses, and daily gain in weight occurred until the 36th day. On the 39th day there was evidence of the onset of labor. The animal was seized at intervals of a few minutes with fits of straining and squatted in characteristic posture while contraction of the abdominal muscles persisted. A bloody vaginal discharge appeared. Palpation of the abdomen immediately excited prolonged muscular contractions. A hard fetal head was wedged above the symphysis. During the next 2 days contractions became irregular, although readily stimulated by touching the abdomen. The bloody discharge persisted. The animal failed to eat. About 54 hours from the time the onset of labor was observed, the nose of the fetus was completely extruded. Marked moulding of the cephalic region of the fetus in its passage through

the pelvis gave evidence of the dystocia. The fetus weighed 88 gm., and the crown-rump length was 130 mm. Thus, the fetus was born on the 41st day, or 55 hours after the onset of labor had been noted.

A second fetus remained undelivered, although palpable above the symphysis. The blood-tinged discharge continued. Straining occurred on abdominal palpation. The animal failed to eat, grew weaker and died on the 47th day. At autopsy a second fetus was found in the birth canal, arrested in descent at the pelvic brim.

With regard to the relation of changes in the fetus to the onset of parturition, it was clearly evident that neither the prolonged survival of the fetuses for a period of 3 days past term, nor their subsequent death in the uterus, was effective in inducing parturition.

The postmature fetuses played an important part in the ultimate outcome of pregnancy in animals with prolonged gestation. In view of the advanced development of the skeletal tissues there was corresponding resistance to autolysis and to reduction in size of the fetus. In addition, the thin-walled uterus was distended more than normally by the excessively large fetuses. It was not surprising, therefore, to find anatomical evidence of injury and even necrosis of the uterine wall. Associated with these changes there was marked impairment of the mechanism of labor, leading to the permanent retention of the fetuses in some animals (table 1, second half).

Placenta and ovaries

The prolonged retention of the fetuses past term in the present experiments gave an unusual opportunity to observe the length of time during which the placental function was adequate to support fetal life. Survival of fetuses about 3 days past term or until the 36th day indicated the functional reserve of the organ.

After death of the fetuses and the consequent interruption of the fetal circulation to the placenta, it was found that the placenta remained implanted in the uterine wall. The duration of the period during which attachment of the placenta persisted was indicated in placentae expelled at parturition on the 41st day, in which there was fresh blood in the vessels of the maternal surface of the placenta. Histological examination confirmed the macroscopic findings. In no. 21, in which postmature macerated fetuses were expelled on the

41st day, placentae were obtained immediately after extrusion from the vagina and fixed in absolute alcohol. Microscopic examination revealed glycogen deposits in the placenta. In view of the rapid disappearance of glycogen following interruption of the circulation, it was evident that the placentae were still receiving a blood supply from the maternal circulation.

Although the placentae were found attached to the uterus long after the death of the fetuses in prolonged pregnancy, there were marked degenerative changes in the organ. In animals in which placentae were retained *in situ*, autopsy on the 49th day (no. 68-2), 51st (no 70-2) and 60th day (no. 58) showed merely fragments of necrotic tissue in sections through the placental area.

Examination of the ovaries in the present experiments showed that failure of parturition at term was always associated with the appearance of a fresh set of corpora lutea. The abdomen was opened and the ovaries and uterus were exposed through a lower midline incision in 27 animals. Without exception there was a fresh set of corpora lutea in the ovaries in addition to the older set which dated from the time of mating. In 9 of the 27 animals, abortion of the entire litter had occurred. In the remaining 18 animals, pregnancy had been prolonged, abortion of part of the litter occurring in 7 of them.

Absence of ovulation after coitus

Prolongation of the period of inhibition to ovulation following coitus was observed in the entire series of animals including those in which there was abortion of the entire litter. Normally, ovulation after coitus fails to occur during pregnancy (Hammond, p. 66). After birth of the litter, however, the inhibition to ovulation is released and copulation followed by ovulation may occur on the day of parturition. In the present experiments, however, instead of release of the inhibition to ovulation about the 32nd day, the occurrence of ovulation after coitus was not observed before the 39th day, or 14 days after injection of urine extract. Even though abortion of the entire litter occurred 2 or 3 days following injection and there were no fetuses in the uterus, ovulation after mating was not noted before the 39th day (tables 1 and 2). (In 2 animals of a later series not in the table, ovulation occurred after coitus on the 39th day, or 14 days after in-

jection.) In animals in which the fetuses were retained in the uterus past term, ovulation following mating was observed as early as the 40th day in 4 cases (nos. 42-2, 23, 25, 81). For example, in no. 25, a litter of 10 postmature macerated fetuses was born in the morning 40 days following mating, and 15 days after injection. Mating on the same day was followed by pregnancy.

Absence of pituitrin effect

Injection of pituitrin in animals in which the fetuses were not expelled at term revealed a striking functional alteration of the uterine

TABLE 3

Absence of pituitrin effect on the uterus in prolonged pregnancy

RABBIT NUMBER	STAGE OF PREGNANCY AT INJECTION	AMOUNT OF PITUITRIN INJECTED	PARTURITION
	days	*units*	
73	33	21.0	Negative
51-1	34	25.0	Negative
22-1	34	10.55	Negative
65	36	6.5	Negative
21	41	1.0	Immediate
68-2	45	19.0	Negative
27	50	20.65	Negative
48	93	22.15	Negative
	Controls		
41	29½	12.0	Negative
48	31	1.0	Immediate
52	31	0.15	After 2 hours
47	31½	0.05	Immediate
57	32	0.05	Immediate
48	32	0.025	Immediate

muscle. Massive doses of pituitrin failed to induce emptying of the uterus on the 33rd, 34th and 36th day of pregnancy (table 3). For example, no. 51-1, weighing 4.4 kg., received 25 international units of pituitrin on the 34th day of pregnancy, but no fetuses were expelled. The pituitrin (20 units = 1 cc., Parke, Davis & Co.) was administered intravenously in 9 injections at intervals of about half an hour over a period of 5 hours, beginning with 0.05 unit and gradually increasing the dose to 12.8 units. A week later, on the 41st day, 5

postmature macerated fetuses were extruded. In normal controls at term, immediate expulsion of the litter began, following injection of 0.05 or 0.025 unit, or one-thousandth the dose ineffective in no. 51-1 (*cf.* Knaus, 1926).

Prolonged retention of fetuses

There remains to be considered the group of animals in which the fetuses were not expelled within about 15 days following injection (table 1, second half). In 19 cases in which fetuses were retained longer than 44 days, the outstanding characteristic was the irregularity both in onset and duration of emptying of the uterus. A clue to understanding the variations in different animals was suggested by the evidence of functional and anatomical alteration of the uterine wall. The blood supply and nutrition of the uterus were obviously modified by the extreme distention with large postmature fetuses that were unusually resistant to autolysis, in view of the advanced development of the skeletal tissues. Another factor to be borne in mind was that in this group of animals there was necrosis of the placenta and retrogression of the corpora lutea. In view of the striking increase in growth and blood supply of the uterus which normally marks the development of the corpora lutea and especially the growth of the placenta, it was interesting to note the condition of the distended uterine wall coincident with the degeneration of these structures.

In this group necrosis and perforation of the uterine wall were noted in animals which died with peritonitis while postmature, mummified fetuses were still in the uterus. Death occurred on the 54th day (no. 27), 60th (no. 58), 143rd (no. 41), and 154th (no. 48). In no. 56 laparotomy on the 53rd day showed extreme distention of the uterus with a hard fetal mass. The uterine wall was much altered in appearance by discolored areas with sticky surfaces. At one region the wall was completely destroyed, exposing the fetal mass. Three weeks later a second laparotomy showed a wall of dense adhesions surrounding the fetal mass. In the ovary a fresh set of corpora lutea was seen, coitus having occurred on the 65th day. The animal was still alive in apparently good condition 198 days after pregnancy began.

In animals in which there was evidence of less extensive injury of the uterine wall, disintegration of the fetuses and gradual emptying of

the uterus occurred slowly. Examination of the uterus, while still distended with necrotic fetal tissue, showed discolored patches like fatty accumulations, 1 cm. or more in diameter, in the wall and along the mesometrial border, *e.g.*, on the 51st day (no. 63), (no. 70-2), on the 52nd day (no. 64). Ultimate emptying of the uterus and repair was revealed by the subsequent occurrence of another pregnancy. Thus, fertile mating was observed in no. 63 on the 89th day following the onset of the prolonged pregnancy, in no. 64 on the 115th day, no. 65 on the 59th day, no. 51-1 on the 55th day, no. 19-1 on the 62nd day, no. 47 on the 133rd day, no. 55-2 on the 71st day. In other animals pregnancy had not recurred after an interval of several months, *e.g.*, in nos. 49, 19-2, 22-2, and 51-2.

Histological examination of the ovaries showed that retention of the fetuses for indefinitely prolonged periods occurred despite retrogression of the corpora lutea. Evidence of the functional state of the ovary was afforded by the occurrence of ovulation following coitus while postmature macerated fetuses were still in the uterus, *e.g.*, on the 46th day (no. 68-2), 51st day (nos. 70-2 and 64), and 65th day (no. 56).

Pituitrin in massive doses failed to induce expulsion of the fetuses on the 45th day (no. 68-2), 50th (no. 27), and 93rd day (no. 48) (table 3). In no. 68-2, 19 units of pituitrin intravenously failed to induce emptying of the uterus on the 45th day. On the 46th day ovulation occurred following coitus while the fetuses and necrotic placentae were in the uterus.

In the group of animals, therefore, in which the uterus failed to empty itself for a period indefinitely prolonged beyond 44 days, there was evidence of alteration of the uterine wall beyond the limits normally observed during the reproductive cycle and pregnancy. When distended with postmature fetuses, it was found that emptying of the uterus became increasingly complicated following necrosis of the placenta and regression of the corpora lutea.

DISCUSSION

The foregoing observations are a record of the termination of pregnancy in animals which received a single injection of about 1 cc. of extract of urine. By this means ovulation was induced about the 25th day of pregnancy, so that at the normal end of gestation on the 32nd

day, the new set of corpora lutea had reached the stage of maximal size and function. In these animals normal parturition at term failed to occur. In the majority of cases, pregnancy was prolonged beyond term. In the remaining cases, abortion occurred. In spite of maximal distention with fully mature fetuses which remained alive in the uterus for about 3 days past term, the uterus failed to expel its contents. Except for inertia of the uterus, pregnancy appeared normal. The placentae remained attached long after death of the fetuses. The onset of parturition in prolonged pregnancy occurred most frequently about 15 days following induced ovulation. Pituitrin was tried, but massive doses at term failed to initiate parturition and merely demonstrated the profound alteration of the uterine muscle. Evidence of the functional alteration of the ovary was afforded by the observation that the period of inhibition of ovulation following coitus, which normally ends at term, was prolonged at least a week past term. The duration of the changes just mentioned, namely, the deferred onset of parturition, the prolonged period of inhibition of ovulation, and the failure of the uterus to respond to pituitrin, corresponded in general to the life span of the experimentally induced set of corpora lutea. When it is remembered that in the rabbit the corpus luteum is active for 14–16 days (Bouin and Ancel, 1910; Hammond, p. 67; Knaus, 1929), even though pregnancy does not occur, it is evident that changes observed in the animals of the present experiments conform chronologically to the normal physiology of the corpus luteum.

In about half of the cases of prolonged pregnancy emptying of the uterus was not completed promptly, but was delayed for a period of days, or even failed to occur. In these animals there was evidence of an additional factor, namely, injury of the uterine wall.

In the abortions observed in the present experiments there were certain distinctive characteristics. The fetuses were cast out alive, or usually not macerated, and vaginal bleeding was profuse at times after separation of the placentae. Only part of a litter was involved in many instances, while the rest of the litter survived in the uterus and eventually reached postmature stages of development. Abortion of the entire litter was seen more frequently in primiparae than multiparae and seemed related to dosage and stage of pregnancy at the time of injection. The onset of abortion occurred after a latent period of

more than 24 hours following injection. In this connection it is interesting to note that, according to Knaus (1929), an interval of about 32 hours elapses following coitus before there is evidence of the onset of activity of the corpora lutea as shown by altered contractility of the uterine muscle and slight histological changes in the endometrium. In the present experiments the brief duration of the period of abortion, which was limited to the 2nd and 3rd day after injection, was also a regular finding. Similarly, termination of pregnancy following hypophysectomy about the 25th day has been observed to be marked by the abortion of living or non-macerated fetuses 2 or 3 days following operation (Firor, 1933; White, 1932). On the other hand, following ovariectomy at this stage of pregnancy, abortion was noted within about 2 days, but macerated fetuses were extruded (Hammond, p. 190; Knaus, 1930). It was interesting, therefore, that coincident with the early stage of proliferation of the induced corpora lutea there was a tendency toward the interruption of pregnancy which resembled the effects noted after hypophysectomy at this phase of gestation.

The alterations in the terminal phase of pregnancy produced under controlled conditions in the rabbit bring to mind certain complications of obscure etiology in women. Missed labor was described as early as 1847 by Oldham. A full-term fetus was retained in the uterus for several months after its death, during which time uterine inertia persisted. Missed abortion was noted in 1868 by Matthews Duncan. He described a delay of many months in emptying of the uterus following death of the fetus at an early stage, and clearly distinguished this condition from incomplete abortion.

In the usual course of abortion in women, two characteristics are noteworthy in connection with the present experiments: first, the delay in expulsion of the product of conception after death of the embryo; second, the coincident ineffectiveness of pituitrin. Streeter (1930) has shown that the death of the fetus between the 6th and 17th week of pregnancy is not followed by emptying of the uterus at once, but as a rule the dead fetus and the placenta are retained about 6 weeks. At this stage of pregnancy there is a large corpus luteum and the placenta has not attained its full size. It is a clinical observation that retention of the fetus at this stage is associated with

refractoriness of the uterine muscle to pituitrin in contrast to the striking effect at term. It will be recalled that in the presence of active corpora lutea in the rabbit pituitrin failed to induce emptying of the uterus, even at term. In the light of these facts, one may view the latent period of about 6 weeks as a measure of the interval which is required for changes in the placenta and retrogression of the corpus luteum to reach the stage at which the uterine muscle is released from the inhibiting influence which normally is operative throughout pregnancy, preventing escape of the fetus from the uterus.

In women, intrauterine lithopedions have been found only in rare instances (Kuchenmeister, 1881, Werth, 1913) although lithopedions associated with ectopic pregnancy are not uncommon.

In the rabbit it has been found that normally pregnancy terminates a considerable time before the fetus has attained the maximal size and development which is possible in the intrauterine environment. With regard to the limits of postmaturity in man, Nürnberger (1927) has pointed out that the birth of a living child later than 302 days from the time of conception is exceedingly rare. In a study of development of excessive size in the fetus, Zangemeister and Lehn (1918) have found that 7000 grams is approximately the limit of weight compatible with normal birth and survival.

Concerning the changes which can be discerned in the rabbit as the end of gestation is reached, there is no support in the present experiments for the view that changes in the fetus incite the onset of parturition. It has been shown, too, that the placenta has sufficient reserve to remain functional for a considerable period past term. Despite the presence in the uterus of postmature fetuses of excessive size, the effect of maximal distention on the plain muscle and nerve elements of the uterine wall has been found insufficient to induce parturition. Indeed one is led to quite another point of view regarding the mechanism of parturition. Throughout the entire course of pregnancy the uterus, unlike other hollow organs of plain muscle, retains its contents. Finally, in a few hours, the long retained fetal body is expelled. Knowledge of the control of parturition seems to be not so much a question concerning the mechanism of expulsion of the contents of a hollow muscular organ, involving only a few hours, as it is a matter of accounting for the failure of the uterus to empty itself throughout the long period of gestation.

In the light of the present observations it is clear that hormonal control is a major factor in retention of the fetus. In the rabbit the importance of the corpus luteum in preventing escape of the fetus from the uterus has been illustrated at length in the present experiments. Emptying of the uterus fails to occur until termination of the life cycle of the corpus luteum. The time of onset of parturition in the rabbit is thus related to the regular rhythm characteristic of gonadal function. A glimpse is obtained of the mechanism upon which one relies in confidently predicting the onset of parturition at the predestined time fixed for the species.

Concerning hormonal control, it may be noted also that, with the growth of the placenta following implantation, the retrogression of the corpus luteum is retarded so that the life span is extended to 32 days instead of 16 as in the non-pregnant rabbit. On the other hand, removal of the corpora lutea or ovaries is followed by interruption of pregnancy. Similarly, hypophysectomy is marked by retrogressive changes in the corpora lutea and prompt termination of pregnancy. It seems necessary, therefore, in the rabbit, to consider the corpus luteum, placenta and anterior hypophysis, in order to describe how the uterus functions in parturition.

In brief, the uterus serves for the retention of the fetus during the period of gestation, and then suddenly functions in the expulsion of its contents. Thus, parturition involves a period of transition from the quiescent to the expulsive phase of this muscular organ. Experimental addition of fresh corpora lutea in the ovary adds to the duration of the quiescent phase, the prolongation of pregnancy being proportional to the life span of the induced corpora lutea.

SUMMARY

The rôle of corpora lutea in parturition was studied by induction of ovulation during pregnancy by means of urine extract so that at term there was a fresh set of corpora lutea at the stage of their maximal activity. Under these conditions the following observations were made.

1. Normal parturition at term was never observed.

2. In most animals, pregnancy was prolonged, the onset of parturition being delayed until 15 days after injection (i.e., the 40th day), or until the end of the life span of the induced corpora lutea.

3. Retention of postmature fetuses longer than the life span of the induced corpora lutea was associated with injury of the uterine wall.

4. Pituitrin administered at term, failed to induce parturition despite a dosage 1000 times greater than the amount normally effective.

5. Fetuses survived in the uterus 3 days past term, *i.e.*, 35 days, and developed to excessive size.

6. An estimate of the functional reserve of the placenta at term was afforded by the extent of development of postmature fetuses and the persistence of glycogen in the placenta at 41 days.

7. By varying the stage of pregnancy at injection, dosage, and parity of the animal, a method was found by which pregnancy was prolonged in 20 cases of the series of 23 animals, while abortion of the litter occurred in only 3.

8. In case of abortion the fetuses were expelled either alive, or before any maceration had taken place. The abortions were limited in their occurrence to the 2nd or 3rd day after injection.

9. There was no support in the results of the present experiments for the view that the onset of parturition is caused by changes in the fetus, senility of the placenta, or mechanical distention of the uterus.

10. Retention of the fetus in the uterus, in the rabbit at least, is under hormonal control. Termination of its retention coincides with termination of the life cycle of the corpus luteum.

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DEATH OF FOETUS IN UTERO

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The occurrence of premature death of the foetus *in utero* prior to the onset of labor is observed somewhat frequently by the practising physician. In certain cases the cause of death can be accurately determined and is attributable to such maternal conditions as syphilis or eclampsia. However, it often happens that the child succumbs *in utero* without discernible cause, and even after delivery a careful autopsy may not reveal adequate reasons for the unfavorable outcome. In an effort to clarify the problem, to obtain the incidence of definitely attributable causes, and to determine to what extent there seems to exist no definite cause, it seemed proper to analyze all cases of foetal death *in utero* prior to the onset of labor occurring in a large series of consecutive deliveries effected on one service under comparative conditions. The results of such an investigation are submitted in the present paper.

Incidence. From the time of its inception in 1896 to January 1, 1932, approximately 25,000 women were delivered on the Obstetrical service of the Johns Hopkins Hospital. In 306 instances, the child succumbed *in utero* prior to the onset of labor, an incidence of 1.2 per cent, or 13 in every 1000 cases. It seems probable that the true incidence of this condition was even higher, since many cases were discarded because the information contained in the records was insufficient to determine accurately whether foetal death had occurred prior to or during the first stage of labor. An incidence of 1.7 per cent was obtained by Rosensohn on all deliveries at the New York Lying-In Hospital for the year 1924, his figures being based on the number of stillborn foetuses with definite maceration.

Race. Although it would be of interest to correlate foetal mortality with the nationality of each parent, the records of the patients' ancestry were not complete enough to enable any noteworthy deduc-

tions to be made and hence it is only possible to distinguish between white and colored women. There were 86 white and 220 colored patients, a ratio of 1 to 2.6. This is a significant difference, since the clinic material was divided almost equally between the two races, and is chiefly explainable in terms of the greater prevalence of syphilis in the colored race, and also in the poorer care which the pregnant negress gives herself during the antepartum period. The latter cause is probably a small one compared with syphilis, which occurs four times as often in the black clinic patients as in the white.

Age. The age of the mother differs very little from the mean figure for the general clinic population and is 22.65 years. The age of one patient was not known. Twelve were young primiparae, *i.e.*, sixteen years of age or younger, the youngest being a colored girl of thirteen years. The oldest patient was forty-nine years of age.

Age distribution of patients in series

YOUNG PRIMIPARAE	17 TO 19 YEARS	20 TO 24 YEARS	25 TO 29 YEARS	30 TO 34 YEARS	35 TO 39 YEARS	40 YEARS AND ABOVE
12	77	105	46	31	20	14
3.93%	259 or 84.92%				34 or 10.82%	

The great majority of eases, 259, or 84.92 per cent, fall within the ages of 17 to 34 years inclusive, which are roughly the figures for the Clinic, so that the age of the patient *per se* could not be said to have any bearing on the intrauterine death of the foetus. The prevalent idea that death *in utero* is more apt to occur in women nearing the end of their childbearing career did not hold true in this series. Smith, referring to Charpentier's Cyclopedia of Obstetrics and Gynecology. quotes Jacquemier as saying that "a woman loses a foetus with greater ease the nearer she is to the age when woman's aptitude for conception usually ceases." The above figures do not confirm this statement for death *in utero* after the period of viability of the child has been reached; however, it may hold good for abortions.

Parity. Peckham's statistics show that in 15,358 consecutive cases delivered in the Johns Hopkins Hospital, 8,404 were primiparae as contrasted with 6,954 multiparae, a ratio of 6 to 5, the greater number of primiparae being due to the fact that it is the policy of the Clinic

to accept all such patients but only those multiparae presenting some abnormality such as pelvic dystocia, abnormal presentation, or toxemia of pregnancy. In this series, foetal death *in utero* occurred in 126 primiparae and 180 multiparae, a ratio of 5 to 7, which is significantly different from the total clinic figures. Thus it is found that in a clinic population whose $\frac{\text{Primipara}}{\text{Multipara}}$ ratio is $\frac{6}{5}$, 70 per cent more than the expected number of intrauterine deaths occurred in multiparous women. The cause of such a discrepancy is not clear.

Duration. In this paper, ten lunar months have been taken as the basis for a full-term pregnancy, and no cases are included which were of less than twenty-eight weeks' duration, since the latter are classified as abortions. Each estimated duration of pregnancy is counted to the time of delivery and not to the estimated date of death of the foetus. In most of these cases, the distinction was almost negligible, as it will be seen that in the majority of the patients labor supervened within fifteen days after the foetal death. There were 5 patients whose pregnancy went past the estimated date of confinement and varied from 7 to 21 days of postmaturity.

Duration of pregnancy

POSTMATURE	FULL-TERM	9½ MOS.	9 MOS.	PREMATURE			
				8½ mos.	8 mos.	7½ mos.	7 mos.
		10	38	30	67	28	22
5	106	195					
1.6%	34.8%	63.6%					

From the above chart it may be seen that foetal death occurred before term was reached in almost two-thirds of the patients in the series.

Retention in Utero. The chart presented below represents as accurately as possible the length of time between foetal death *in utero* and the onset of labor. In many cases, 145 out of the 306, it was impossible to determine because of incomplete available information just how long the foetus has been dead. In 2 patients, labor set in within 24 hours after the death of the foetus, one being a case of premature separation of the placenta, and the other a case of typical eclampsia.

Retention in utero

UNKNOWN	LESS THAN 24 HOURS	1 TO 7 DAYS	8 TO 14 DAYS	15 TO 21 DAYS	22 OR MORE DAYS
145	2	83	36	23	17
		121 (75%)		40 (25%)	

The longest period of retention was 61 days. Another patient went 52 days with a dead foetus in the uterus; six went 40 to 48 days; six, 30 to 36 days; and three, 22 to 28 days. Of the 161 in which the time of foetal death was definitely known, 121, or 75 per cent, went into labor within two weeks, while in 40, or 25 per cent, 15 to 61 days elapsed before delivery was effected.

Streeter found that in 437 specimens ranging from the seventh to the seventeenth week of pregnancy and including only cases in which there were fairly reliable clinical records of menstrual age, the duration of retention following foetal death averaged from 30 to 56 days. His calculations were based on the discrepancy between the menstrual age of the foetus and its actual age in size as determined from a growth curve calculated in terms of crown-rump length and weight of the embryo. It seems probable that earlier foetuses might well be retained longer than those nearer term, since their small size would be less likely to stimulate the uterine muscle to contract, and also that the longer, more rigid lower uterine segment and cervical canal of the early pregnant uterus would respond less readily to uterine contractions.

That the death of the foetus *in utero* bears any relation to the onset of labor pains can not be deduced, although it should be noted that in 14 cases of typical eclampsia, those patients in whom labor was not induced usually were delivered within a day or two after the death of the foetus. Since our knowledge of eclampsia and the cause of labor is totally inadequate, one cannot say that intrauterine death was responsible for the onset of labor rather than some oxytocic circulating in the blood of the eclamptic woman.

Sex. The sex of the foetus was studied with interest in view of the fact that statistics show that more boys are born than girls. Rauber, in 1900, pointed out that the birth ratio of boys to girls was 106 to 100. Schultz, in 1921, showed that the ratio in early abortions was

slightly greater, being 110 males to every 100 females. He found that for stillborns the sex ratio decreased to 88 for the sixth month, but then increased rapidly to 112 for the seventh month, to 123 for the eighth month, and 156 for the ninth and tenth months. Crew, in 1927, found a still higher ratio at the onset of pregnancy, and estimated a conception ratio of at least 170 males to 100 females. Streeter and Schultz, after examining a large number of early abortions, believe that this figure is far too high, since it is difficult to determine the sex of an early abortion, and they feel that many specimens are classed as males which under careful embryologic study would prove to be females. Since this series includes chiefly premature, a smaller number of full-term, and a few postmature infants, one would naturally expect a ratio somewhere between the estimates of Rauber and Schultz or even an approach to the former's ratio. Omitting 14 cases in which no information concerning the sex of the foetus was available, there were found 162 males as compared with 130 females, giving a sex ratio of approximately 125, which corresponds to Schultz's figures for the eighth month of pregnancy.

Signs and symptoms. The signs and symptoms of death *in utero* are usually quite definite and clear-cut. Of the 306 cases here studied, 122 patients were able to give the number of days in which no foetal movements were felt. Many of these were seen several days before the onset of labor and the diagnosis was confirmed by failure to hear foetal heart tones, or by making other observations indicative of intrauterine death; while in others, the patient's statement was thought to afford a reliable criterion. Aside from the mother's failure to feel the foetus move (122 cases), in 64 the diagnosis was made some days before the onset of labor because of failure to hear foetal heart tones independently or in conjunction with other signs indicative of intrauterine death. There remain 120 cases in which the diagnosis of death *in utero* was not made until after the onset of labor or even until after the delivery of the foetus; but that death *in utero* did occur before the onset of labor is thought definite, since no case has been included where the labor was protracted and the maceration only slight.

Probable signs. Clinical signs indicative of death of the foetus *in utero* before or during labor include the following: absence of foetal heart tones, failure of the examiner to elicit active movements of the

foetus, inability to palpate the foetus satisfactorily due to its flabby condition or loss of tone (Spalding's "foetal collapse"), a softened foetal head, crepitation of foetal skull-bones on abdominal or vaginal palpation, and decrease in the size of the uterus since a previous examination.

Suggestive signs. Frequently the diagnosis of death *in utero* was made probable at the time of the rupture of the membranes, when a deeply stained and not infrequently foul-odored amniotic fluid escaped. The x-ray, showing the disorderly arrangement and overriding of the skull-bones, was used in only three cases in this series, and in each the characteristic signs of Spalding were present. Spalding reported 21 and Horner 3 cases, both in 1922, in which a correct diagnosis of death *in utero* had been made by means of the x-ray. Both concluded that a positive diagnosis could be made by such means and Spalding felt that his characteristic picture was the only pathognomonic sign of intrauterine death. He found overlapping of the foetal cranial bones, asymmetry and a decrease in the size of the foetal head. In his controls of living foetuses he found no such overlapping except as a result of the compression of labor and never noted a shrinkage of the skull contents. On the other hand, Stein and Arens four years later demonstrated with x-rays of living and dead foetuses the difficulty of making a roentgenographic diagnosis of death *in utero* independently of clinical data.

A valuable addition to our armamentarium for diagnosing intrauterine death is the Ascheim-Zondek test. Unfortunately the test was not employed in any of the cases of this series, but it has since been used and is a considerable aid in making a positive diagnosis of death *in utero*. Frank states that death of the foetus does not affect the result of the test so long as the products of conception are retained in the uterus, even for weeks or months. Mazer and Goldstein find that the test is unreliable and reason that so long as there is vascular contact between the placenta and uterus, the hormones of pregnancy are produced and the test remains positive, while Guttmacher feels that such will be the case so long as there are living trophoblastic cells in the body. However, the last observer has obtained three correct negative tests out of four cases in which dead foetuses were suspected, while the fourth case was one in which the foetus was suspected of

having been dead for five days before the last of three tests was made. Apparently, a negative result in a suspected case is definite evidence of actual death *in utero*, whereas a positive test is of no import.

In 1921, Baer found in 44 women at or near term a basal metabolic rate 33 to 35 per cent above normal and reported one case with a rate of only plus ten when there was a dead foetus *in utero* at the thirty-sixth week of pregnancy. He concludes that foetal death *in utero* in late pregnancy "is detectable in a woman otherwise normal by a drop in B.M.R. compared with the average in this series." Apparently no further work has been done along this line, but it seems probable that such a test would be of some diagnostic aid providing it may be assumed that the rate would decrease after intrauterine death, as Baer, Stander and Peckham have found it to fall during the first ten to fifteen days of the puerperium.

Polak stated that acetonuria is always found following intrauterine foetal death. This test was done on only a few cases in this series with a very small percentage of positive results. Likewise, King and others report that acetonuria is not a constant finding.

Guirauden has made the observaton that foetal intrauterine death may be diagnosed by the coagulation time of the maternal blood, and states that the longer the foetus has been dead the shorter will be the coagulation time. According to this author, a diagnosis of death *in utero* is confirmed if the coagulation time approaches five minutes at any stage during the last three months of pregnancy, while during the earlier months it is even longer and often as much as ten minutes. It is difficult to consider this test trustworthy in the last three months of pregnancy, since five minutes is well within the normal limits of coagulation time. Furthermore, the author does not report any tests done on normal pregnant women with living foetuses.

Johnston has made observations on cases of death *in utero* and found in his series that the mother almost invariably gave a history of hyperactivity of the foetus a short time before the cessation of foetal movements. He attributed this condition to the final struggle of the foetus in the advancing or terminal stages of asphyxia. On reviewing the literature, we find that this point is mentioned by Torland, Stein and Arens, King, and F. J. Browne. Johnston also noted that soon after intrauterine death the uterine souffle became more pronounced. It

would seem that this increase in intensity of the uterine souffle might be only relative due to the fact that the foetal sounds were absent and hence left only the maternal sounds to be heard. Moreover, in auscultating the pregnant abdomen no attention is ordinarily paid to the maternal sounds, they being ignored in the search for the foetal tones; hence after foetal death the former would be more noticeable.

Williams noted that an indication of missed labor is often found in retrogressive changes in the breasts, which become soft and flabby.

Drosin gave two procedures which have been of great value to him in establishing the viability of the foetus. First, he placed the patient in the dorsal recumbent position, directed her to exhale and to suspend respiration for as long a period of time as possible. This procedure was repeated in rapid succession for ten to fifteen times so that the oxygen supply of both mother and foetus was diminished and the carbon dioxide content of the blood increased. Normally, he states, foetal movements will become increased because of the partial asphyxia. The second procedure consisted in stimulating movement of the foetus by grasping the anterior foetal shoulder and pressing it upward and backward.

Other interesting and suggestive but not pathognomonic symptoms are maternal chills and fever, nausea, malaise, headaches, fetid breath, bad taste in the mouth, epigastric distress, discomfort suggestive of gastric ulcer, or dragging lower abdominal pains.

Causes of death. The actual cause of death *in utero* is often difficult to determine. In 229, or 74.75 per cent of the cases in this series, one or more assignable causes of death were found. These are grouped under three main divisions: (1) foetal complications; (2) maternal complications; and (3) other causes.

Deaths attributable to foetal complications

Syphilis	130
Anomalies of cord	19
Hydramnios	13
Anomalies of foetus	5
Total	167

Syphilis. In this series syphilis played the major rôle, there being 130 deaths directly attributable to this complication. In only three of

the luetic mothers in this series were lesions present; in each case a secondary rash. The remaining 127 were instances of latent syphilis and of these women 92 had positive Wassermann reactions, 14 had had positive Wassermanns rendered negative by treatments before delivery, while 21 had no Wassermann records but were thought to have syphilis because of proved disease in the foetus. It may be noted in passing that, among those infants born alive but with congenital syphilis, more males than females succumb during the first few weeks of life, as is indicated in the accompanying chart.

Outcome to syphilitic foetuses

	STILL-BIRTHS	BORN ALIVE	NEONATAL DEATHS	DISCHARGED ALIVE
Males	82	23	13	10
Females	48	20	8	12
Total	130	43	21	22
Sex Ratio	171	115	162	83

No explanation is evident why males should be more susceptible to syphilis than females, during both intra- and extra-uterine life, unless one theorizes in terms of factors which cause more males than females to be lost throughout the intrauterine period from all causes. For an explanation one would have to look to genetics and assume that the male is inherently weaker or less stable by virtue of having only one active sex chromosome, (the female having two active sex or x-chromosomes); just as Bridges found a greater instability in individual fruit flies which had more than the customary number of either sex chromosomes or autosomes.

Cord anomalies. Speculation as to the cause of foetal intrauterine death other than syphilis is rather wide and varied. One death in the series was associated with a very short cord (the exact measurement not given), and this was believed to have been at least a contributory cause of foetal death. Nickoff reports one instance of intrauterine death due to a short cord which was wrapped twice around the neck. In our series there were 15 cases in which the cord once around the neck was mentioned and another with three coils. Many writers consider that coils of cord around the neck, arm, leg, or body are causes of foetal death *in utero*. One eight months' foetus in our

series showed a true knot in the cord, this knot being drawn fairly tight and probably causing death *in utero*. F. J. Browne has reported two cases of a true knot in the umbilical cord evidently responsible for foetal death, and has collected from the literature, chiefly French and German, 26 similar cases. In this series it was frequently noted that the cord showed various twists and torsions but no stress was laid upon that finding as it was felt that they were produced after death. It does not seem reasonable to suspect that the pulsating umbilical vessels or the normal tone or elasticity of the cord would allow the occurrence of sufficient twisting to encroach upon the lumina of the vessels and obstruct their circulation, unless some other condition, such as an unusually short cord, were also present. Schauta reports a case in which he counted 380 twists in the cord, but infers that they were produced after intrauterine death. King and Pfeiffer recognize torsion of the cord as a cause of death. Williams believed that true knots were occasionally pulled taut enough to cause asphyxia of the foetus, that occasionally loops of cord caused strangulation, but that rarely was torsion so marked as to interfere seriously with circulation. However, one must consider torsion or twisting of the cord as a possible cause of death *in utero*, since there is no dependable method whereby one can determine whether these phenomena are produced before, during, or after foetal death.

Our series included one case with a constricted area in the umbilical cord and this will be discussed later. Browne reports a case of localized constriction of the cord near the foetal end, which he believes due to an obliterative endarteritis, the primary involvement being in the intima and adventitia of the vessels with the fibrosis then spreading to the Whartonian jelly and giving the typical constriction. King also reports a case in which was found a single umbilical artery associated with a generalized torsion of the cord.

Hydramnios was found with syphilis in 6 instances, with partial premature separation of the placenta in 1 case, and with no other pathological change in 4 instances. The hydramnios cannot be blamed entirely in each case for the foetal death but it is felt that the combination of hydramnios and other pathological conditions in most cases renders the supposition more likely.

Foetal anomalies. There was a surprisingly small number of foetal

deformities or anomalies causing death *in utero* in the series. It is probable that the anomalous foetuses succumb much earlier in pregnancy than those that are included in this study; and that if they were strong enough to survive the abortion age there would be no reason why they should not go to term. We report only five instances of foetal malformation and these include one spina bifida and one neck tumor, each with syphilis, one totally cleft palate, one sacrococcygeal tumor with hydramnios, and one child showing absence of the left eye. This last case was found in association with a papyraceous foetus. It cannot definitely be said that the observed anomaly was the direct cause of death, but in four of the five cases there was associated some other pathological condition, and it seems reasonable to consider that the several combined conditions rendered the foetus incapable of survival.

Foetal deaths attributable to maternal complications

Toxemias	48
Cardiac disease	6
Upper respiratory infections	5
Focal infections	4
Pyelitis	3
Anomalies of uterus	2
Tuberculosis	1
Diabetes mellitus	1
Lobar pneumonia	1
Total	71

Toxemias of pregnancy. Excluding syphilis the toxemias form the largest group of maternal disease complicating the cases of death *in utero*, with a total of forty-eight. These are subdivided accordingly: unclassified toxemias, 10; typical eclampsia, 14; low reserve kidney, 10; chronic nephritis, 13; preëclampsia, 1. That the foetal mortality in the toxemias, especially chronic nephritis and eclampsia, is high and intrauterine death not infrequent, needs no further comment. Intrauterine death of the foetus in eclampsia occurred much more frequently than our figures would indicate and a number of such cases are not included, since it could not be determined from the records whether or not the child succumbed prior to or early in labor.

Cardiac disease. Death of the foetus with retention *in utero* oc-

curred in six mothers with cardiac disease. Williams did not commit himself, but stated that many authors ascribe considerable significance to valvular lesions of the maternal heart and believe that the death of the child is attributable to deficient oxygenation of the maternal and hence the foetal blood.

Upper respiratory infections. The ability of upper respiratory infections to produce intrauterine foetal death *in utero* is still a debatable subject. We, however, list in our series two cases of maternal bronchitis and two of acute tonsillitis. Another mother had had an acute upper respiratory infection some time before the onset of labor, and had felt no foetal movements subsequent to the attack, though she recovered and went into labor spontaneously later on.

Focal infections. There were two instances of gonococcal arthritis and one of otitis media in the series. Another mother had acute inflammatory rheumatism and the cause of foetal death was believed to be due to the medication rather than to the toxins or to the infecting organisms themselves, salicylates having been given in large doses.

Pyelitis. There were also three instances of antepartum pyelitis.

There is much discussion in the literature on foetal death due to the toxins of maternal disease or to the infecting organisms themselves. Among those recognized by Williams and DeLee are scarlatina, typhoid, cholera, pneumonia, plague, streptococci causing erysipelas, colon bacillus, anaerobic bacilli, all pus-forming organisms, and any organisms causing maternal septicemia. Lobenstine reported a case of intrauterine death caused by a retroplacental blood clot which became infected with the bacillus of Welch, but whether the foetal death was due to separation of the placenta or to the infection with the gas bacillus was not proved, as no bacteriological study was done on the foetal organs. DeLee reports two cases in which the foetus succumbed before the onset of labor, and the organs of each contained a pure culture of streptococci. The first mother had been well except for a slight pharyngitis, not cultured, and the second had a negative physical examination but gave a history of a previous septic puerperium. W. H. Browne and Kincaid report a case of death *in utero* at term, with a pure culture of hemolytic streptococci obtained from the heart blood of the foetus. An attempt to prove the origin from a maternal source was unsuccessful, as urine, blood, and throat cultures were

negative. They report, then, a clinically healthy mother whose foetus apparently succumbed *in utero* to a hematogenous streptococcal infection. Spies collected two cases of intrauterine death in which a chronic peritonitis was found. Thus it would seem from a résumé of current literature that maternal infections bear an important influence on foetal viability, even *in utero*, with transmission of a generalized or a focal infection taking place from the maternal to the foetal circulation through intact vascular channels. From a practical standpoint it impresses the importance of prenatal care, and even such momentarily insignificant disabilities as sore throats and colds should receive the most careful attention.

Anomalies of uterus. Abnormalities of the uterus accounted for two deaths in the series with one case showing an eight months' pregnancy in an incarcerated uterus and another foetal death in the rudimentary horn of bicornute uterus.

Tuberculosis and pneumonia. One patient had pulmonary tuberculosis and another had lobar pneumonia with asphyxia probably the cause of death *in utero* in these cases.

Diabetes. Although we found in our series one foetal death *in utero* attributable to either maternal diabetes or an unclassified toxemia, or more probably to both, foetal deaths attributable to maternal diabetes alone have been reported by Lambie, F. J. Browne, and others. Lambie, quoting Chapiet, says that the foetal mortality including not only deaths *in utero* but also deaths during labor is estimated at about 50 per cent. Chapiet's article was published in 1907.

Other maternal diseases. Dorman states that another maternal disease causing foetal death *in utero* is pernicious anemia in which the child is apt to succumb near term. Phosphorus, lead and coal gas poisoning may often result fatally to the unborn child, though the mother survives. This author also believes that in exophthalmic goitre foetal asphyxia may result from improper oxygenation of the maternal blood due to thyroid pressure on the trachea. It seems doubtful, however, that such asphyxia would be severe enough to cause foetal death and not terminate the life of the mother. Seitz gives hyperthyroidism as a cause of intrauterine death while Litzenberg and Carey have shown that hypothyroidism is not only a cause of sterility and of abortions but also of deaths *in utero*.

FOETAL DEATHS ATTRIBUTABLE TO OTHER CAUSES

Hemorrhage. Hemorrhage was responsible for the death in 8 cases, four being due to placenta praevia, and a like number to premature separation of the normal implanted placenta. Hemorrhage, of course, occasions the death of a large number of foetuses, but most of these succumb after the onset of labor and are not included here. The fatal hemorrhage in the above eight cases occurred from three hours to forty-two days before the onset of labor.

Bodily violence. Most authors are rather skeptical as to the possibility of an act of violence to the mother resulting in the intrauterine death of the foetus. Rosensohn is the only writer who believes that a fall or blow may result fatally to the child. In this series, there were 7 instances where it would seem that violence obviously had some bearing upon the death of the foetus. The injuries were usually falls resulting in violence to the distended abdomen such as falling against a bed, door, rock, or down stairs. In what way the act of violence should in each case cause death is not obvious, and it does not seem plausible that it should be due to direct trauma to the foetus. The most probable cause, one might suppose, would be a premature separation of the placenta. In three cases of this group a deeply stained fluid was expelled a short time after rupture of the membranes and this might have been a mixture of old blood with amniotic fluid.

Induction of labor. It is important to note that in 4 instances foetal death occurred during attempts to induce labor. One patient received castor oil and quinine six days before the actual onset of labor with unsuccessful result, and she was not observed during the administration of the drugs. Subsequently, labor set in spontaneously, a dead child was diagnosed, the labor was short, and a badly macerated foetus was delivered.

Gellhorn reports one case of his own and one each of F. W. Lynch and J. L. Baer in which the cause of foetal death *in utero* was obviously castor oil and quinine. Torland attempted to induce labor on a patient by giving 60 cc. of castor oil and two hours later 10 grs. of quinine. Shortly thereafter the woman developed a marked skin rash, oedema of the eyes, a temperature of 104°, headache, tinnitus, deafness and slight dyspnoea. After taking the quinine, she felt repeated strong foetal movements and an hour later, on examination, no foetal heart

tones were heard nor movements felt or heard. In a series of 765 patients in whom quinine was used for the induction of labor, Dilling and Gemmell found that the drug was apparently responsible for 8 deaths *in utero*, or 1.04 per cent of the total. In each fatal case, foetal heart tones ceased to be audible within thirty-six hours after the administration of the quinine, a time within the limits of the maximal concentration of the drug in the maternal blood. The maximum was reached six to eight hours after administration, but the period of high concentration not uncommonly lasted for thirty-six hours. None of the above patients evinced any idiosyncracy to the drug, as the only symptoms noted were slight nausea and vomiting, or tinnitus, and these were no more severe than in those women whose foetuses did not die in the uterus. This would seem to indicate that it is not necessary for the mother to have an idiosyncracy for quinine in order that the foetus should succumb *in utero*. As early as 1878, Porak, and in 1880, Runge, commented upon adverse effects to the foetus *in utero* when quinine was administered to the mother, and found that after the administration of the drug the amniotic fluid was frequently stained with meconium, that the babies frequently became jaundiced, and that they did not thrive as well after delivery.

The other three intrauterine deaths in our series attributable to induction were in cases which were given one or more trials of the Watson technique, when the foetal heart failed to be heard or movements felt after some one of the injections of pituitrin. Here the tetanic contractions of the uterus resulting from the intramuscular injection of pituitrin were responsible for asphyxia and intrauterine death.

Unusual smallness of placenta. Holland suggests that unusual smallness of the placenta may be a cause of intrauterine death when the foetus attains a size that requires a greater placental blood supply than can be furnished. He has no idea as to the etiology of the condition but believes it is responsible for the death of 10 out of 17 cases in his series, to which no other cause could be assigned.

Lethal mutations. A factor which should not be overlooked, though little understood at present, is that of dominant lethal mutations. Muller has shown in his work with the fruit fly that in approximately one of every thousand cases certain definite mutations arise. He has also shown that some of these, though a very small proportion, are so

detrimental to the inheriting individual that it is never born alive and hence cannot reproduce, and is lost to genetical study. It seems probable that such changes may also occur in the human race, since the same basic genetical principles apply to both, the greatest difference being that inheritance in man is much more complex due to the larger number of chromosomes, there being twenty-four pairs in man and only four pairs in the fruit fly, a fact which would suggest that there is a much greater probability for mutations of both non-lethal and lethal type in man.

Summary of actual and contributory causes of foetal death

Foetal deaths attributable to foetal complications	167	
Foetal deaths attributable to maternal complications	71	
Foetal deaths attributable to other causes	19	
Total	257	
Omitting duplications	28	
Total cases with an assignable cause of death	229	(74.75%)
Total cases without any assignable cause of death	77	(25.25%)

Assembling our figures then, and subtracting the 28 cases which were included in more than one group, there remain 229, or 74.75 per cent of the total, for which an actual or a contributory cause of foetal intrauterine death was found, and 77 or 25.25 per cent for which no assignable cause was evident. The records indicate that adequate prenatal care would probably have prevented some of these deaths; however, many were due to unpreventable or unavoidable accidents.

Mortality and morbidity. In the above series there were four maternal deaths. Two of these were due to tuberculosis and lobar pneumonia, respectively. A third patient developed a severe intrauterine infection following spontaneous delivery and died with generalized peritonitis. The fourth fatality was in a case of preëclampsia, delivered following induction of labor by a Voorhees bag and developing a mixed puerperal infection resulting in death. At autopsy there was found a thrombosis of the innominate vein and right carotid artery. Thus, we have a gross maternal mortality of 4 or 1/8 of 1 per cent, and a corrected mortality of 2 or 1/16 of 1 per cent, excluding deaths due to pneumonia and tuberculosis. However, no fatality occurred which was directly attributable to the dead foetus *in utero*.

The puerperal course of one patient was unknown as she left the hospital shortly after delivery and was not followed at home. Two hundred and twenty-two patients were afebrile and 71 developed puerperal infection, an incidence of 23.25 per cent. This is a higher figure than that obtaining for the general clinic population which is 17.75 per cent. There were also eleven instances of intrapartum infection, an incidence no greater than that in the total clinic.

Induction of labor. Induction of labor was resorted to in only 26 cases of this series, and of these the indication for this procedure in most instances was not the diagnosis of death *in utero* but an underlying condition such as a severe toxemia or postmaturity. These twenty-five comprise only the successful inductions and do not include the few noteworthy unsuccessful attempts which were discussed earlier in the paper. It has been the policy of the Clinic not to induce labor on a patient because of the presence of a dead foetus in the uterus, but rather to allow her to wait and go into labor spontaneously, unless other symptoms developed warranting evacuation. Occasionally, however, such a procedure may become necessary because of the upset mental status of the patient due to her knowledge of the death of her child. In our experience, there seem to have been no untoward symptoms following the delivery of a foetus some time after its death, and we do not believe that intrauterine death of the child is in itself an indication for the immediate termination of the pregnancy.

It seems to be a common belief that soon after the foetus dies the patient will promptly and automatically go into labor. This was, to some extent, the case in our series. There were only 161 cases in which the exact number of days from the death of the child to the onset of labor was known; and of these, 85, or 52.5 per cent, went into labor within the first seven days after death *in utero*, and 121, or 75 per cent, within the first fourteen days. Among the latter there were many instances of toxemia; but there were no toxemias among the 17 cases in which the child was retained in the uterus for as long as twenty-two days, and none of the latter showed any severe symptoms, either basic or as a result of the death of the foetus. This would seem to indicate that the toxemic cases compensate not only by having relatively short labors, but also by going into labor soon after foetal

death. It is known that almost immediately after intrauterine foetal death in a case of toxemia of pregnancy, the patient usually shows marked improvement. Lobenstine, however, reports one case where a toxemic patient grew profoundly worse following the intrauterine death of the foetus.

As has been said, there is usually no necessity for rapid delivery in otherwise normal patients and it is rarely necessary even to induce labor in such a patient. The anxiety of the mother, as mentioned above, may sometimes necessitate action from the attending physician. On the other hand, Smith urges induction of labor and delivery as soon as it is definitely known that the child has perished, since he believes that from the dead foetus the mother might absorb toxins resulting in death, which would have been prevented by the timely emptying of the uterus. However, he reports three cases, none of which showed any remarkable signs of toxic absorption from the dead foetus.

The methods of induction of labor employed in the cases of the series were varied. In 9 instances the Wales bougie was employed and in each case the pains resulting were poor in character. A Voorhees bag or a Champetier de Ribes balloon was used in five cases and here, too, the resulting pains were not totally adequate. In five cases castor oil and quinine alone were employed, with the resulting pains described as poor or fair, at best. Those cases in which pituitrin was used either intramuscularly or intranasally showed the strongest pains. The optimal methods of induction hardly warrant discussion, as the condition of the patient should govern the type best suited for the individual case. The only difference between these cases and those of living foetuses lies in that one might be allowed the freer use of pituitrin since only the condition of the mother has to be considered. We mention pituitrin because it seems to have given the most satisfactory results; however, its use should be judicious and especially so in the case of toxemias.

Labor pains. A consideration of the labors in terms of their strength, effectiveness, frequency, and duration of pains indicated that in 88 instances these were poor, weak, irregular and generally ineffectual; while in 80, they could be classified as fair; in 135 (45 per cent) as good, or relatively effectual. It seemed rather surprising that there were not more than 88 unsatisfactory labors out of the

total 306 cases. One might suspect that with such a flabby, toneless mass as the dead foetus in the uterus, the pains would be rendered much less effectual than when the intrauterine contents were of better consistency; yet such was not the case in our series. In many of the unsatisfactory labors, however, the uterine contractions were extremely ineffectual and were stimulated very little by the use of a bougie, bag, castor oil and quinine, or pituitrin given either intranasally or hypodermically. In three instances only was Caesarean section practised.

Postpartum hemorrhage.[1] Since we have come to think of the uterus containing a dead foetus as having a relatively poorer tone than normal, we would expect some increase in postpartum hemorrhage due to atony. There were 286 cases in the series which showed a blood loss of less than 600 cc. Eight women had had antepartum hemorrhages. There were twelve instances of postpartum hemorrhage described in the records as being due to uterine atony, an incidence of 1 in 25 cases, which is definitely lower than that of the general clinic population. Apparently the smaller number of cases of postpartum hemorrhage observed in this series is due to thrombosis of the vessels at the placental site occurring after foetal death.

Foetal presentations. For the sake of comparison we list the foetal presentations observed in the series and compare them with the incidence found in the general clinic population. In 15 cases the presentations could not be determined from a study of the records. Of the remaining 291 in which the position was determined there were:

			Incidence in series	*Incidence in general clinic population*
Vertex	234		80.35%	94.6%
Breech	48		16.55%	3.9%
Transverse	8	9	3.1%	0.96%
Compound	1			

From a comparison of these figures it would seem that when the child dies *in utero* the incidence of breech presentation becomes five times as frequent as usual, and transverse and compound presentations occur four times as often. However, since the mean age of the foetuses in this series is about eight months and since breech presen-

[1] In this series the arbitrary standard of 600 cc. or more of blood loss as constituting a post-partum hemorrhage has been used.

tations are somewhat more common at this time than in full-term pregnancies, our figures are affected to an unknown extent by this factor.

Placentae. Since the early cases in the series were not followed as closely with regard to routine examination of the placenta as is now the case, we find a record of only 216 of the 306 placentae or approximately two-thirds of them. Of these, 103 were described as macroscopically normal, and 113 as abnormal. Such gross changes as infarcts of the placenta, calcification, fibrosis, etc., are omitted on account of their relative frequency and slight influence on the foetus except where enough tissue was thrown out of function to cause a serious decrease in the placental blood supply. There were 14 non-syphilitic and 62 definitely syphilitic placentae, as determined by microscopic examination. Two of these latter also showed tumors, one containing microscopic chorionic cysts and vascular obliteration, and the other a subchorionic cyst, which was syphilitic in spite of a negative maternal blood Wassermann and was from a case of hydramnios. The remaining large number of 140 were diagnosed as questionable syphilis. However, a study of the placentae gave no added valuable information.

Recurrences. Finally, we wish to discuss the possibility of premature death of the foetus tending to recur with succeeding pregnancies. Obviously the probability will depend upon the cause of the intrauterine death and to a certain extent can be answered with a relative degree of accuracy. If the patient has syphilis and continues to avoid regular treatment, she may expect the tragedy to recur at least in some future pregnancies. If a patient should happen to repeat a toxemia of pregnancy in a later confinement, a recurrence of the accident is likely, particularly if there be present a chronic nephritis. The length of the cord in later pregnancies cannot be predicted, but there is no reason to expect the cord of each pregnancy to be excessively short or unusually long and to become wrapped about the foetal parts so tightly as to interfere with the foetal circulation. Likewise, foetal anomalies, hemorrhage due to either placenta praevia or premature separation of the placenta, or a true knot in the cord having occurred once would not seem to predispose the patient to a second similar mishap. Those cases due to methods of induction, especially with

massive doses of quinine and pituitrin, are now avoided by the well informed physician. Acts of violence will continue to take their toll so long as the pregnant uterus becomes exposed to such dangers. The prognosis, therefore, will depend entirely upon the individual case and its etiology, each presenting a complete problem in itself, except for patients with nephritis or syphilis. The other cases would seem to present only the chance of the law of average, and 306 cases in 25,000 deliveries would represent the probability of the recurrence of premature death of the foetus *in utero*. Habitual death *in utero* occurs very occasionally and warrants radical treatment to procure a live baby. Ballantyne reported a remarkable case of a twenty-nine year old working woman who had had three previous pregnancies terminated by death *in utero* between the twenty-eighth and thirty-second week of gestation. He was able to carry the fourth to term and deliver the patient of a live child after eight weeks' rest in bed, with the administration of calcium, arsenic, iron and strychnine.

CONCLUSIONS

1. The incidence of foetal death *in utero* during the last trimester of pregnancy in a series of 25,000 consecutive deliveries was 306 or 1.2 per cent. The incidence is higher in the colored than in the white race with a ratio of 2.6 to 1.

2. The age of the mother has no influence on death *in utero*, although with multiparity the incidence increases.

3. The majority of intrauterine deaths occur some weeks before the estimated date of confinement.

4. Those patients with acute toxemia of pregnancy usually fall into labor soon after intrauterine death of the foetus, while the duration of retention following foetal death due to other causes is usually longer.

5. More males than females die *in utero*, the sex ratio being 125.

6. Signs and symptoms of foetal death *in utero* are usually clear-cut, and consist of failure of the mother to feel foetal movements, cessation of the foetal heart, absence of normal foetal body tone, boggy foetal head, crepitation of foetal skull-bones, and retrogressive changes in the size of the uterus.

7. Further suggestive signs and symptoms often occur and include maternal nausea, malaise, headaches, foul breath, bad taste in the

mouth, hyperactivity of the foetus followed by cessation of foetal movements, a pronounced uterine souffle, a fall in basal metabolic rate, and retrogressive changes in the breasts.

8. Helpful adjuncts to diagnosis, but not altogether reliable or pathognomonic, are found in the Ascheim-Zondek test and in the x-ray.

9. Acetonuria is not a constant finding. The clotting time of the maternal blood would seem to be of no value.

10. The causes of intrauterine death in order of their frequency were: syphilis; toxemia of pregnancy; loops of cord about some foetal part; intercurrent maternal disease; acts of violence to the pregnant abdomen; induction of labor; hemorrhage; foetal anomalies; true knots in and torsion of the umbilical cord; unusual shortness of the cord; localized constriction of the cord; incarceration of the uterus; and uterine anomalies.

11. Male foetuses seem to be more susceptible to syphilis and succumb to it more readily than do female.

12. The gross maternal mortality in the series was 1/8 of 1 per cent and the corrected mortality 1/16 of 1 per cent. The morbidity rate was high and was 23.25 per cent as contrasted with 17.75 per cent for the general clinic population.

13. It is seldom necessary, from the standpoint of the patient, to induce labor because of foetal death *in utero* and rarely, if ever, necessary to effect a hasty delivery.

14. The character of labor pains was not significantly different from those of the patient with a living foetus.

15. The incidence of postpartum hemorrhage was lower in the cases of intrauterine death than in the general clinic.

16. Abnormal presentations such as breech, transverse, and compound occur more frequently following death of the foetus *in utero*.

17. Except when death has been due to syphilis or nephritis there seems to exist no increased chance of a second premature foetal death *in utero* for the patient.

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EXPERIMENTAL EXOPHTHALMOS AND HYPERTHYROIDISM IN GUINEA-PIGS

Clinical Course and Pathology

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It is a well established fact that the functional state of the thyroid gland can be greatly influenced by the anterior hypophysis. Ablation of the pituitary gland causes a retardation of development or an atrophy of the thyroid gland (1, 2, 3, 4, 5, 6), and also a significant decrease in the basal metabolic rate (4, 7, 8). These changes can be prevented by the injection of an extract of anterior pituitary substance (4, 5, 9).

It is also well recognized that injections of anterior pituitary extract stimulate the functional activity of the normal thyroid gland. By virtue of this property, such extracts initiate metamorphosis in larvae of axolotls and accelerate it in the larvae of frogs and salamanders (10, 11, 12, 13, 14, 15, 16). This phenomenon is invariably accompanied by parenchymal hypertrophy with hyperplasia of the thyroid gland (13, 14, 15, 16, 17, 18) and an increase in oxygen consumption (19).

The injection of potent anterior hypophyseal extracts also induces the following changes in birds and mammals:

(1) Parenchymal hypertrophy and hyperplasia of the thyroid gland with liquefaction and loss of colloid (20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34), all of which eventually recede in spite of continued injections of the extract (20, 26, 27, 34). The ability of the anterior pituitary extract to produce these changes is probably seriously impaired by heat (29, 32, 33, 45). Although there is some dispute (29, 31, 35, 36) concerning the specificity of changes in the thyroid

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gland and the effect exerted upon it by non-specific proteins, it is generally agreed that even if the latter have any influence, they certainly do not induce a deviation from the normal which is comparable to that elicited by anterior pituitary extracts.

(2) Hypertrophy of the Golgi apparatus of the thyroid gland (30).

(3) An initial increase in basal metabolic rate (31) which spontaneously returns to its normal level in spite of uninterrupted injections of the extract (37, 38). This rise in basal oxygen consumption can be prevented from the very beginning (39) or decreased after it has become elevated (40) by the oral administration of potassium iodide. Siebert and Smith (37, 41) have recorded a single composite curve depicting the *average* oxygen consumption of several guinea-pigs under treatment with anterior pituitary extract, but their data do not reveal the individual variations nor the effect of injections continued for more than twenty-eight days. The latter is also true of Anderson and Collip's results (38).

The rise in the basal metabolic rate is known to be directly dependent upon the presence of the thyroid gland and can not be provoked in its absence (22, 31).

(4) Decrease in total and protein-bound iodine in the thyroid gland simultaneously with their increase in the blood stream (42, 43, 44, 45, 57, 58).

(5) Exophthalmos in metamorphosing tadpoles (11, 12) as well as in ducks and guinea-pigs (26, 46). This exophthalmos can be produced in the absence of the thyroid gland (47) and disappears during anesthesia and with death (26, 46).

(6) Tachycardia (33, 48) and abnormal nervous irritability (48) in guinea-pigs.

NATURE OF THE PRESENT INVESTIGATION

The purpose of the present observations is to record a detailed study of the clinical course of an experimental syndrome in guinea-pigs which can be induced by daily intraperitoneal administration of potent extracts of the anterior hypophysis. Special reference is directed to the behavior of the basal metabolic rate, the pathological changes in the thyroid gland which are coincidental with its variations, and the rela-

tion of exophthalmos to changes in the rate of oxygen consumption and histopathology of the thyroid gland.

METHOD AND MATERIALS

Male and female guinea-pigs weighing between 400 and 650 grams were thoroughly acclimated to an environmental temperature of 26° to 30°C. and maintained on a constant diet.[2] The dry food mixture and water were constantly available to the animals except for the 17 hours of starvation preceding determination of the basal metabolic rate. During this time they had access only to water for 15 hours.

The basal metabolism was determined in a modified Benedict closed circuit apparatus at the critical temperature (32°C.) for the guinea-pig (30, 31). With occasional exceptions (*vide infra*), these animals usually become almost motionless in the animal chamber long before the temperature equilibrium of the apparatus is established (60 minutes). The rates of oxygen consumption, which are recorded for two or three consecutive 15-minute intervals, are often identical, and most of the experiments check within 2 to 5 per cent. A few experiments are included which checked within 10 per cent. The basal oxygen consumption is calculated from the average of these periods in terms of cubic centimeters per square meter (Meeh's formula) per minute, and is 105 for the male and 99 for the female, with a maximal variation of ±10 per cent. Several successive determinations on individual guinea-pigs in this series checked within ±3 per cent in the majority of cases. A few results, however, checked between ±4 and ±7 per cent.

The anterior pituitary extracts employed in these studies were prepared by E. R. Squibb and Sons, Parke, Davis and Company, and the Schering-Kahlbaum Corporation.[3] Two of the preparations (Squibb and Parke, Davis) were alkaline extracts originally prepared for the

[2] The diet consisted of a dry mixture of whole ground wheat (5000 grams), alfalfa meal (5000 grams), flaxseed oil meal (500 grams), $CaCO_3$ (85 grams), NaCl (50 grams), and Mead's powdered whole milk (1000 grams) in addition to small amounts of fresh lettuce twice weekly.

[3] I wish to express my appreciation to Dr. J. A. Morrell (E. R. Squibb and Sons), Dr. E. A. Sharpe (Parke, Davis and Company), and Dr. Gregory Stragnell (Schering-Kahlbaum Corporation) through whose generous coöperation a constant supply of extracts was made available for this investigation.

growth-promoting stimulus which they impart to the white rat, while the "thyreotropic hormone" (Schering) was reported by its distributors to be free of this property. A limited number of experiments to check these claims yielded results similar to those reported by these three pharmaceutical firms.

All injections were given intraperitoneally in daily doses of 1 cc. to 4 cc. of the extract prepared by Squibb, 1 cc. of that of Parke-Davis, and 0.0025 to 0.010 gm. of the Schering-Kahlbaum preparation.

The 36 guinea-pigs included in this investigation were studied over periods varying from 48 hours to 190 days. Determinations of the basal metabolic rate were usually made on three alternate days in order to establish a base line. Basal weights and rectal temperatures were recorded before each determination. Six normal animals were used for controls on the histologic studies. Five guinea-pigs are still being studied. The remaining 25 animals were sacrificed or died at intervals during the experimental period. A complete autopsy and microscopic examination of all endocrine tissues were made of the latter group, but only the pathological changes in the thyroid gland are being presented in this paper. It is interesting to note, however, that all three extracts caused a rapid and striking enlargement of the adrenal cortex simultaneously with their characteristic effect upon the thyroid gland.

RESULTS

The Basal Metabolic Rate. The behavior of the basal metabolic rate following daily uninterrupted injections of one of these anterior pituitary extracts is characterized by three distinct periodic variations.

In the *first period* there is a prompt marked increase in the basal metabolic rate, starting sometime within 24 to 48 hours and reaching its highest value (+26 per cent to +60 per cent) between the seventh and fourteenth day of treatment. The rapidity with which the maximal elevation is attained, and the height to which it goes, seem to depend only in part on the quantity of the daily dose of extract, because in individual cases the response may be sharply curtailed from the very beginning (4B ♀, 9♂).

During this period the basal pulse rate increases approximately 30 per cent, and the basal weight decreases to a point from 6 per cent to 27

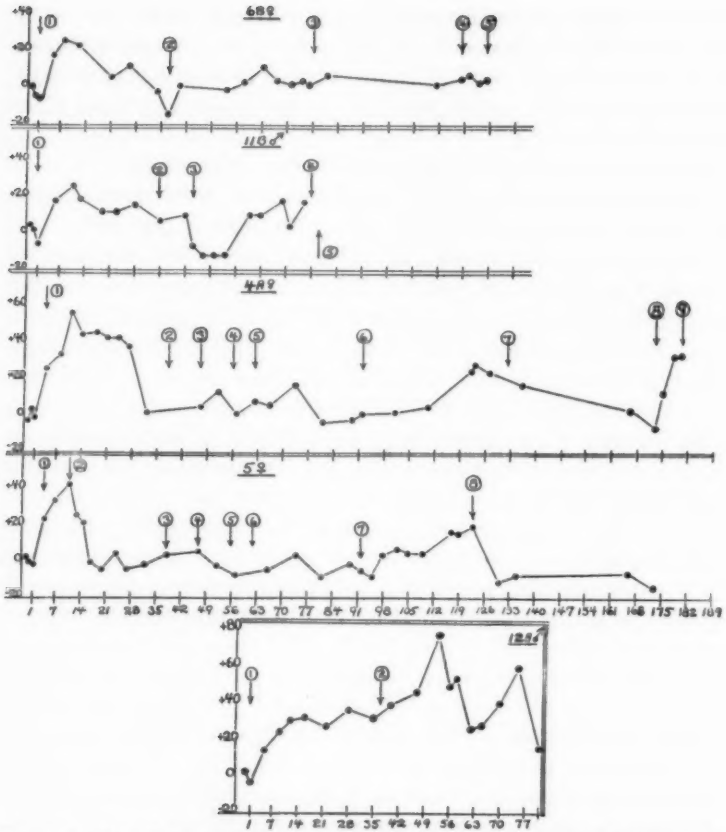

CHART 1. THE EFFECT OF VARIOUS EXTRACTS OF THE ANTERIOR HYPOPHYSIS ON THE BASAL METABOLIC RATE OF NORMAL GUINEA-PIGS

Abscissae: Experimental period in days; *Ordinates:* Basal metabolic rate in per cent.

6B: (1) 2.5 mgm. Schering's extract started; (2) 1 cc. Squibb's extract (second batch) substituted, Schering's extract discontinued; (3) Squibb's extract discontinued; (4) 1 cc. Squibb's extract started again (same batch); (5) Sacrificed.

11B: (1) 2.5 mgm. Schering's extract started; (2) Increased to 5 mgm. daily; (3) 1 cc. Squibb's extract substituted for Schering's extract and 0.05 gm. NaI started intraperitoneally daily; (4) Animal suddenly became ill with pneumonia; (5) Sacrificed.

per cent below the normal level. The subsequent variations of these values parallel the behavior of the basal metabolism rather closely. Although the rectal temperature of the normal guinea-pig may vary a degree or two Fahrenheit from day to day, it is certain that the extract is usually responsible for a significant rise of about one degree Fahrenheit during the initial rise in basal metabolic rate.

The *second period* is distinguished by a striking refractory state or remission which usually develops when the peak of oxygen consumption has been reached. This phenomenon is certainly not due to a progressive decrease in potency of the extract, because previously untreated guinea-pigs respond to the latter characteristically. During the remission the basal metabolic rate returns to normal with varying degrees of rapidity, so that it reaches its original value within one to three weeks. One guinea-pig, a notable exception (12A ♂), has maintained a constantly elevated but fluctuating basal metabolic rate for approximately four months. When the remission is fully established, the basal metabolism may show either a slight transient increase (1BB ♀) or may fall even below its normal level (6B ♀, 5 ♀). Such a decrease suggests that prolonged stimulation may lead to impairment of the normal functional level of the thyroid gland with the development of hypothyroidism.

The *third period* of activity is characterized by a recrudescence of the disturbance in oxygen consumption with another elevation of the basal metabolic rate. Only one factor has been constantly associated with this phenomenon.

4A: (1) 0.5 cc. Squibb's extract (first batch) started; (2) Squibb's extract discontinued; (3) 0.5 cc. Squibb's extract (first batch) started again; (4) 1 cc. Squibb's extract (second batch) continued; (5) Increased to 2 cc. daily; (6) 1 cc. Squibb's extract (third batch) continued; (7) Third batch of extract discontinued; (8) 1 cc. Squibb's extract (third batch) started again; (9) Sacrificed.

5: (1) 0.5 cc. Squibb's extract (first batch) started; (2) 0.1 gm. KI p.o. daily; (3) Extract and KI discontinued; (4) 0.5 cc. Squibb's extract (first batch) started again; (5) 1cc. Squibb's extract (second batch) continued; (6) 2 cc. Squibb's extract (second batch) daily; (7) 1 cc. Squibb's extract (third batch) and 0.05 gm. NaI daily; (8) Extract and NaI discontinued.

12A: (1) 2.5 mgm. Schering's extract started, daily; (2) Schering's extract discontinued, 1 cc. Squibb's extract (second batch) substituted for Schering's extract.

Ordinarily, brief experiments of less than a month's duration were completed with a single batch of extract; but those animals which were treated continuously over a period of months received a fresh supply of a similarly made extract at various intervals. The recrudescences in basal metabolic rate occurred in each instance from several days to two weeks after such a change in extract was made, and daily intraperitoneal injections of 0.05 gm. sodium iodide did not exhibit an inhibiting effect.

These changes can not be ascribed to any known specific quality of the fresh extract, because normal, previously untreated, guinea-pigs reacted to it characteristically. It is also interesting that animals (6B ♀, 11B ♂), which were treated with the Schering preparation until they developed a remission, also experienced this period of exacerbation when their injections were continued with the Squibb extract, and 12A, which up to that time had not developed a remission, responded to this change in therapy by a marked increase in its already elevated oxygen consumption.

Having mentioned this coincidence, it seems fruitless to theorize concerning the cause of this phenomenon until more is known concerning the intrinsic mechanism of the cycle of activity through which the thyroid goes under the influence of various stimulants and depressants.

The Pathology of the Thyroid Gland. The pathological appearance of the thyroid gland during this latter period of recrudescence has not yet been studied, but there is a well defined cycle of histological changes in the thyroid gland coincidental with the initial increase and subsequent remission in basal metabolic rate. During the first 24 to 48 hours (20A ♀), the cells of the acini in the *center* of the gland are hypertrophied, (cuboidal) and the vascularity of the gland increases appreciably. The normal colloid of the central acini begins to lose its firm deeply staining character, becoming rather fluid and partially disappearing from the acinus. These changes may account for its "vacuolization" after fixation and staining. Cellular hyperplasia occurs coincidently with hypertrophy and can be detected, not only by counting mitoses (21, 23) but also by the increased number of cells around an acinus. Groups of closely packed interacinar epithelial cells which appear to be "budding" from hyperplastic acini are also

prominent, and there is a significant increase in the number of acini to a high-power field coincident with an absolute decrease in their diameters. If this stimulation is continued, these changes spread further toward the periphery of the gland. The advanced hypertrophy and hyperplasia finally result in irregularly-shaped acini whose lumina are partially or totally obliterated by invaginations of the lining epithelium (1B ♀, 7A ♂, 6A ♀), while the vascularity of the gland is at its maximum just before this stage is reached. In these cases the colloid is not entirely gone from all the acini, but that which remains is either granular or of a thin, fluid, poorly-staining variety. The individual hypertrophic cells reveal many minute vacuoles scattered throughout their cytoplasm and their inner apices are filled with closely-packed fine granules. The rapidity with which all of the above morphologic changes appear and the intensity which they develop seem to run somewhat parallel with the quantity of extract administered daily.

The isolated foci of lymphocytes which have been observed in the interacinar spaces of normal thyroid glands are not essentially different from those occurring in animals injected with anterior pituitary extracts. In neither case are they characterized by an obvious germinal center.

During the first week or ten days, there is definite correlation between the progressive changes in the histopathology of the thyroid gland and the increasing basal metabolic rate. Loeb, Bassett and Friedman (23), and Eitel and Loeser (33), have demonstrated that definite regressive changes in this pathological state appear rapidly after stimulation with anterior pituitary extract is discontinued and the known period of hyperfunction is over. They have found that a firm, deeply staining, normal-looking colloid reaccumulates almost completely within six days and a large portion of the parenchymal hypertrophy and all of the hyperplasia disappear within seven (33) to eleven days (23) after the anterior pituitary extract has been discontinued.

It is therefore probably of importance that two animals (16B ♀, 19C ♀) revealed only insignificant involutionary changes in their acinar colloid and little regression of the parenchymal pathological process when their basal metabolic rates had been *decreasing spontaneously* for a week in spite of uninterrupted injections of the anterior pituitary extract. The pathological findings in these two cases were

indistinguishable from those observed in animals with a *progressively increasing* basal metabolic rate.

If one insists that cellular hypertrophy and hyperplasia always represent hyperfunction, one may still account for the spontaneously decreasing oxygen consumption in these animals by assuming that the effects of the calorigenic hormone were being neutralized by a protective compensatory mechanism or "anti-thyroid substance." However, the experiments of Siebert and Smith (39), and of Krogh and Lindberg (49), do not reveal definite evidence of a similar defense mechanism in guinea-pigs against administration of thyroxin, although Kunde (50) found a slight tendency to spontaneous decrease in oxygen consumption after massive doses of thyroid substance in dogs. Similarly, there is no evidence for the existence of a protective "anti-pituitary substance."

The alternative explanation of this paradoxical situation is that, after a certain period of stimulation, the hypertrophied cell is no longer capable of manufacturing the calorigenic hormone as rapidly as its stimulus demands either because of injury to its protoplasm or exhaustion of its raw materials. This type of hypertrophic and hyperplastic epithelium can not be interpreted in terms of hyperfunction, and at this stage seems to be associated with a *relative functional insufficiency*.

This relative functional insufficiency probably comes on during the first week of the experimental period when the hypertrophic and hyperplastic changes are nearing their greatest development. This allows time for the latent period which usually occurs before the maximal effect of a given amount of thyroxin is elicited, and also for the latent period which follows after it is discontinued and before its effects wear off (49).

Eventually, in spite of uninterrupted administration of anterior pituitary extract, the thyroid approaches its normal appearance (18A ♀, 9♂), and finally becomes, histologically, (1A ♀, 4B ♀, 2AA ♀, 20B ♀) comparable in most respects to the normal controls. 3A's thyroid, which had been stimulated intermittently over a prolonged period, revealed extensive scarring throughout the gland. The histological appearance of this thyroid gland suggests that parenchymal injury may be a factor in producing functional exhaustion.

Further Studies on the Refractory Period. Preliminary experiments on several animals in a refractory state offered the opportunity of studying their ability to respond to further injections of anterior pituitary extract after discontinuance of the latter for a variable number of days.

These studies would indicate that, once an animal has entered upon the refractory period, its thyroid gland may be unable to respond characteristically to further stimulation with anterior pituitary extract. When the extract was discontinued for only nine days, reinjection for eleven days caused a negligible change in the basal metabolic rate (+8 per cent) in one animal (4A ♀) and a sharp decrease in oxygen consumption (27 per cent and 13 per cent) in two other guinea-pigs (3A ♀ and 5 ♀, respectively). Four animals were subsequently allowed to go for 35 to 55 days without extract. Three of these (3A ♀, 4A ♀, 4B ♀) revealed an appreciable increase in basal metabolic rate as compared with their former responses, while a fourth animal (6B ♀) did not show the slightest change in oxygen consumption after injection for eight days.

The unexpected decrease in basal metabolic rate which resulted from reinjection of 3A ♀ and 5 ♀ and their subsequent course (low basal metabolic rate of 5 ♀ and extensive scarring of 3A's thyroid) are further evidence that the refractory period may possibly be due to functional exhaustion dependent upon depletion of the precursors of the calorigenic hormone or actual parenchymal injury. In this connection it is of interest that Verzár and Wahl (31) have demonstrated a substantial *decrease* in the basal metabolic rate following injection of anterior pituitary extract in thyroidectomized guinea-pigs.

Weight Curve. All three extracts were found to have similar *immediate* effects on the weight curves, and if the Squibb and Parke-Davis preparations supplied any growth-promoting stimulus to the adult guinea-pig, it was probably overshadowed by their thyroid-stimulating quality. One animal (10 ♂) did show a slight increase above his original weight after he entered the refractory state. A similar tendency was noted in 6B ♀ whose injections were discontinued while she was in a refractory state and later resumed after 41 days. When the extract was administered for the second time for 8 days, this animal did

not respond to its thyreotropic action (growth-promoting Squibb extract), and although its basal metabolic rate remained essentially unchanged, the weight tended to increase.

There is an obvious individual variation in the course of the weight curve following administration of the anterior pituitary extracts. Some animals lose weight precipitously as the basal metabolism increases, and finally die without having shown the slightest resistance to the effects of the extract, while others do not react so violently to the injections. As a general rule, the initial loss of weight is abrupt, varies between 6 per cent and 27 per cent of the original body-weight, and reaches its lowest level after six to twelve days of treatment. There is no constant quantitative correlation between the increasing rate of basal oxygen consumption and the per cent of weight loss (50). The varying degrees of anorexia that the animals obviously developed at the beginning of treatment may be partially responsible for this discrepancy.

Immediately after the initial weight loss there is a period of recovery during which the animal's weight may remain fairly stationary at its new level, return to its original value, or regain a significant fraction of the latter. Animals surviving for several months tended to regain all of their lost weight, unless the basal metabolic rate became increased again.

EXOPHTHALMOS

Of the 30 animals injected with anterior pituitary extract, 9 developed exophthalmos, and widened palpebral fissures due particularly to retraction of the upper eyelid. Slight prominence of the eyes occurred in several guinea-pigs (3A ♀, 19A ♀, 19D ♀, 23B ♂) toward the tenth day of the experimental period when the most marked hypertrophic and hyperplastic changes are usually developing in the thyroid gland and when the basal metabolic rate is approaching its highest level. The exophthalmos was much more marked when it developed after the animal had entered the refractory period (5 ♀, 10 ♂, 4A ♀, 6B ♀), and striking exophthalmos was seen only in those animals (5 ♀, 4A ♀, 6B ♀) which were injected over a period of several months and especially in those which finally developed abnormally low basal metabolic rates (5 ♀, 6B ♀). Unilateral exophthalmos, right, appeared

in 12A ♂ during the sixteenth consecutive week of injections, although his basal metabolic rate had been +50 per cent two days previously and was known to have been continuously elevated during the first twelve weeks of the experimental period. Only one animal (23B ♂) out of four that received 3 cc. to 4 cc. of the Squibb extract daily for eight days developed a slight transient exophthalmos on the fourth and eighth days.

Anterior pituitary extract (Squibb) produced one instance of striking exophthalmos (5 ♀) in spite of the rapidly decreasing basal metabolic rate following daily oral administration of 0.1 gram of potassium iodide. The proptosis, however, almost disappeared when injections of the anterior pituitary extract and iodide were discontinued for nine days between the 37th and 47th days of the experimental period. It reappeared quickly when the injections of extract were resumed. When the anterior pituitary extract was again discontinued on the 123rd day, during a secondary rise in basal metabolic rate, the latter fell from +20 per cent to −11 per cent, but the exophthalmos remained practically undiminished during the 64 days, although the oxygen consumption was persistently low. The basal metabolic rate was not followed beyond this point, but the animal lived for 82 more days (a total of 146 days without extract) during which time the intensity of the exophthalmos varied considerably and was sometimes quite striking. Similar chronic exophthalmos developed in 4A ♀ and 6B ♀ after 132 and 77 days of injection, respectively. Without extract the exophthalmos in these two animals persisted for 41 days essentially undiminished, but increased somewhat when the extract was readministered.

At one time or another in their clinical course all of the animals mentioned above have shown an essentially unilateral exophthalmos. Whenever the exophthalmos was definitely bilateral, one eye was frequently more prominent. In any event, the exophthalmos in all the animals has shown sudden spontaneous variations in intensity from time to time without obvious reason.

These experiments indicate that the exophthalmos is produced independently of the thyroid secretion which causes the elevation of the basal metabolic rate. These data also suggest that the anterior pituitary extract is more capable of inducing exophthalmos when the animal

is not under the influence of an hyperthyroidism but rather in an hypothyroid state. Our conclusions may explain why a significant exophthalmos does not develop until the animal has at least reached the beginning of its refractory state, and also lends further credence to our views concerning the probable functional insufficiency which exists at certain stages of thyroid hypertrophy and hyperplasia.

The recent experiments of Marine and Rosen (47), who have produced exophthalmos in guinea-pigs following thyroidectomy, substantiate these conclusions. The experiments of Gley (51) and Kunde (50) and the clinical experiences of Zimmerman (52) and Ruedemann (53) have also associated exophthalmos with myxoedematous states.

Activity and Behavior. During the first week of the experimental period there is a marked decrease in activity and a simultaneous diminution in appetite. These early constitutional disturbances wear off if the animal recovers and they are usually replaced by a marked change in behavior. Some of the animals go wild with excitement at the approach of a human hand, and when placed in the metabolism chamber claw and turn about in the limited space until they drop from exhaustion. The only possible way of determining their basal oxygen consumption is under the influence of amytal (54). Other animals betray their nervous state particularly by their lack of patience and restlessness, and when they are in this condition it is more difficult to obtain constant satisfactory determinations of their basal metabolic rate, many of which have to be checked with the animals under the influence of small doses of amytal (54).

A satisfactory quantitative method of evaluating this nervous state has not yet been devised, but it seems probable from observation alone that the increased sensitivity to stimuli persists after the remission in basal metabolism has set in. There is one striking exception to this in guinea-pig number 5 ♀ who became exceptionally docile when her basal metabolism decreased to abnormally low levels even though her exophthalmos remained exceedingly prominent.

Changes in Fur. Soon after the basal metabolic rate starts to increase the guinea-pig begins to shed hair and the normally smooth, glossy fur becomes shaggy and unkempt. This process which is most marked at the height of the increase in oxygen consumption is probably due to thyrotoxicosis (26) and it recedes during the refractory phase.

In two animals with light tan and medium brown coats (12A ♂ and 11B ♂) the lost hair was either replaced or the remaining hair turned extensively black during the experiment.

DISCUSSION

The cycle of events which anterior pituitary extract stimulates in the guinea-pig's thyroid is remarkably similar to that recorded for the thyroid in human exophthalmic goiter by Marine and Lenhart (55) and by Wilson (56).

The clinical course of the basal metabolic rate in exophthalmic goiter is also similar to that of the experimental syndrome in guinea-pigs. Both conditions are characterized by a progressive intensification of the metabolic disturbance until a peak or crisis is reached, after which there is a period of sustained activity which *spontaneously* subsides over a variable length of time. Since the guinea-pig lives his span of life in a small fraction of that allotted to the human being, it is not surprising that the clinical course of the experimental syndrome is expressed in terms of weeks, rather than in terms of months or years as in man. It is also interesting that recrudescences can occur under certain conditions in both instances.

The relation of exophthalmos to post-operative myxoedema in human exophthalmic goiter, and to experimental hypothyroidism in guinea-pigs following thyroidectomy or long-continued injections of anterior pituitary extract, indicates that the *primary cause* of exophthalmos in exophthalmic goiter and the injections of anterior pituitary extract are both capable of producing exophthalmos independently of the calorigenic hormone of the thyroid gland. In fact, Marine and Rosen (47) suggest that the anterior pituitary extract is even more effective in the entire absence of the thyroid gland (48).

Although this study has recorded a remarkable similarity between exophthalmic goiter in man and this experimental syndrome in animals, it is obviously hazardous, at the present state of our knowledge, to identify the pathogenesis of these two conditions with each other.

SUMMARY AND CONCLUSIONS

Simultaneous studies of the basal metabolic rate and pathology of the thyroid gland were carried out on 30 guinea-pigs injected with

anterior pituitary extracts over a period extending from 48 hours to 190 days. Six guinea-pigs were used for controls.

Interpretation of the available data suggest the following conclusions:

(1) These injections produce a syndrome which is remarkably similar to that of exophthalmic goiter in man, but there is no evidence that the pathogenesis of these two conditions is identical.

(2) The behavior of the basal metabolic rate during prolonged injection is extremely variable. It is characterized by an initial increase followed by a spontaneous remission, and may exhibit subsequent recrudescences. The spontaneous remission in basal metabolic rate may be due to a relative functional insufficiency of the thyroid gland (rapid depletion of the stored precursors of the calorigenic hormone with or without parenchymal injury), although the development of a protective "anti-pituitary" or "anti-thyroid" substance must be considered a possibility.

(3) Parenchymal hypertrophy and hyperplasia of the thyroid gland appear simultaneously with systemic evidence of its hyperactivity, but these same pathological changes may still be present when the basal metabolic rate is spontaneously decreasing. In the latter event, this pathological picture is therefore associated with a decreasing activity of the thyroid gland.

(4) Exophthalmos is produced independently of the calorigenic hormone of the thyroid gland. Anterior pituitary extract seems to be more capable of inducing prominent exophthalmos in the absence of hyperthyroidism and in the presence of hypothyroidism. Chronic exophthalmos which persists after the injections are discontinued may result from prolonged administration of the extract.

It is a pleasure to acknowledge my appreciation to Dr. E. K. Marshall, Jr. and Dr. W. T. Longcope for the privilege of investigating this problem and for their constant interest and timely advice. I am also indebted to Dr. E. M. K. Geiling for his many helpful suggestions, to Mr. Max Brödel for his illustration of the exophthalmos and to Mr. Milton Kougl for the photomicrographs.

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PLATE 1

(1) Upper Left: *2A* (×350).
(2) Upper Right: *21A* (×350).
(3) Lower Left: *6A* (×350).
(4) Lower Right: *16B* (×350).

(1) *2A:* Thyroid gland from an untreated guinea-pig; (2) *21A:* 1 cc. Squibb's extract daily, B. M. R. +40% after 4 days; sacrificed on the 5th day; (3) *6A:* 10 mgm. Schering's extract daily, B. M. R. +100% after 10 days, died of thyrotoxicosis on the 10th day; (4) *16B:* 1 cc. Squibb's extract daily, B. M. R. +51% after 11 days, +25% after 18 days; died of thyrotoxicosis on the 18th day.

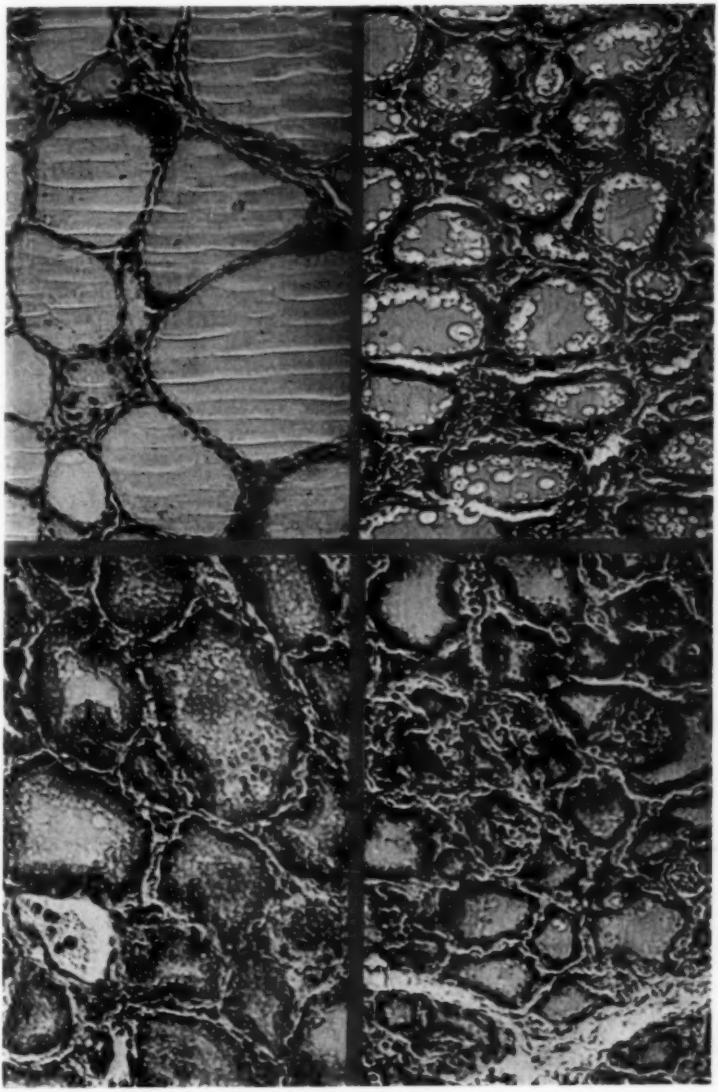


PLATE 2

(1) Upper Left: *18A* (×350).
(2) Upper Right: *3A* (×100).
(3) Lower Left: *4A* (×350).
(4) Lower Right: *6B* (×350).

(1) *18A:* 1 cc. Squibb's extract daily, B. M. R. +62% after 10 days, +5% after 24 days, sacrificed on the 35th day; (2) *3A:* 1 cc. Parke, Davis' extract daily, B. M. R. +70% after 7 days, +25% after 10 days, +7% after 21 days, extract discontinued on the 37th day for 10 days after which the B. M. R. was +13%. 1 cc. Parke, Davis extract changed B. M. R. to +8% after 8 days (54th day), −14% after 11 days (57th day). Extract discontinued for 38 days (92nd day, B. M. R. +4%). 1 cc. Parke, Davis extract changed B. M. R. to +16% after 3 days (95th day), +26% after 6 days (98th day). Died on the 9th day (101st day) weighing 350 grams, original weight 600 grams. This pathological change occurred only once in this series and its significance is regarded conservatively. (3) *4A:* See Chart 1 for details; (4) *6B:* See Chart 1 for details.

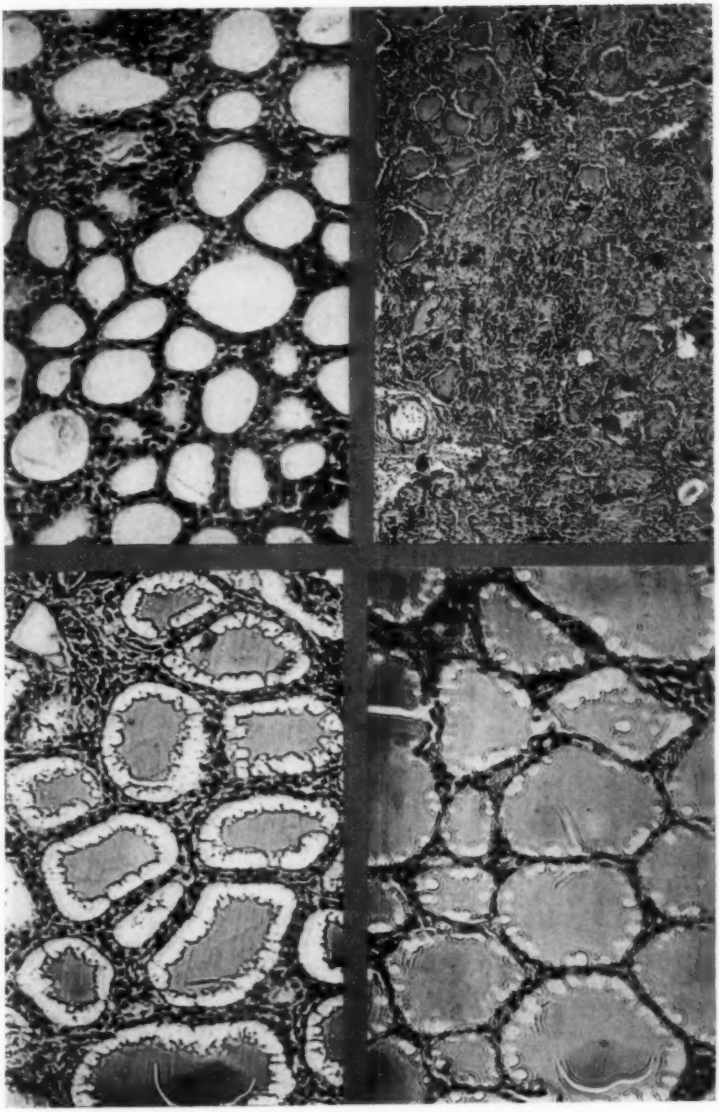
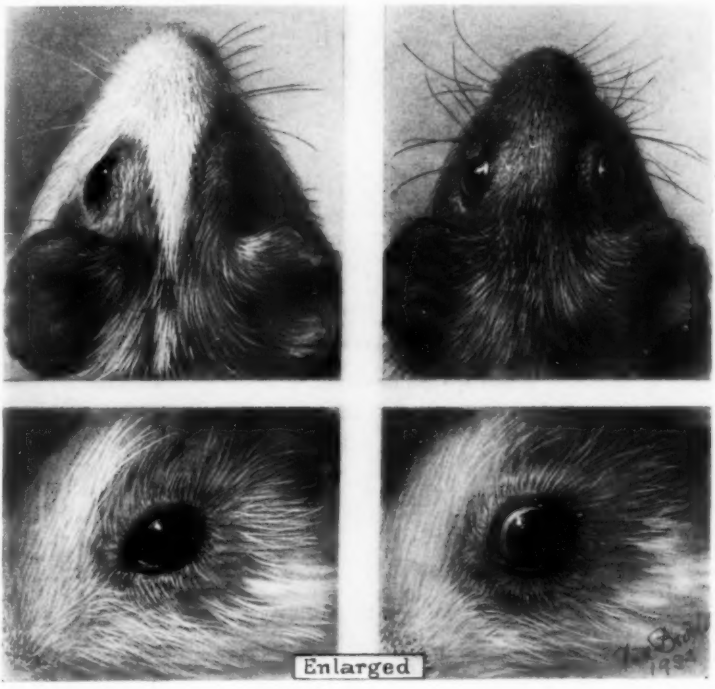


PLATE 3

Upper and Lower Left: Normal appearance of eyes in an untreated guinea-pig as seen from above and laterally.

Upper and Lower Right: Exophthalmos in guinea-pig No. 5 induced by daily intraperitoneal administration of an alkaline extract of the anterior hypophysis (Squibb).


Enlarged

BOOK REVIEWS

Le Sinus Carotidien et la Zone Homologue Cardio-aortique. By C. HEYMANS, J. J. BOUCKEART and P. REGNIERS. 1933. *(G. Doin et Cie, Paris, France, 1933.)*

The work done on the functions of the carotid sinus since Hering's discovery of this region [1923] was summarized by Heymans and his associates in a book published in 1929. The tremendous advances made in this field since that time have necessitated a new edition. The book comprises an anatomical description of the carotid sinus, the physiological, pharmacological and pathological relations, their application to man and their possible clinical significance; with an account of the action of the depressor nerve upon the arch of the aorta. The reference to Magendie and Cooper [1836], which occurs in other texts on the carotid sinus, should be to Cooper [1836]. Magendie did not report his findings on occlusion of the carotid arteries until later, and worked independently of Cooper.

The greater part of the material is based upon experimental work. Heymans developed several technical procedures for the study of the function of the carotid sinus, based upon acute experiments. The necessary correlation of these experiments with those in normal controls is now going forward to some extent.

C. L. G.

Medical Nursing. By DEBORAH MACLURG JENSEN AND JULIUS JENSEN. Illust. 267 pp. $2.50. *(Macmillan Co., New York, 1932.)*

Follows the usual trend of lectures on medical nursing, attempting presentation by the case method. Illustrations are good. Helpful references are given. The style is not particularly good; the information is scattered and sometimes inconsistent.

M. B. D.

Principles and Practices in Public Health Nursing, Including Cost Analysis. [National Organization for Public Health Nursing, Inc.] 129 pp. $1.75. *(The Macmillan Co., New York, 1932.)*

A complete, concise, clear exposition of past and current public health nursing problems and policies, containing valuable information for nurses.

M. B. D.

A Textbook of Medicine for Nurses. By E. NOBLE CHAMBERLAIN. 439 pp. *(Oxford Univ. Press., New York, 1931.)*

A book which presents little that is new and attempts to include rather than to select material. The urine tests, for instance, are better presented in small

laboratory manuals available. Information about nursing care is scarce, incomplete and frequently confused with medical treatment. There are a number of excellent plates, many of them colored.

The book may have some use for supplementary reading, but not as a textbook.

M. B. D.

Chinin in der Allgemeinpraxis. By DR. MED. FRITZ JOHANNESSOHN. 1930. [Unbound.] 232 pp. (*Bureau tot Bevordering van het Kinine-Gebuik, Amsterdam. W.*)

Chinin in der Allgemeinpraxis. By DR. MED. FRITZ JOHANNESSOHN. 1932. [Unbound.] 176 pp. (*Bureau tot Bevordering van het Kinine-Gebuik, Amsterdam. W.*)

Essentially a rapid review, expended in the later work. Valuable for quick reference, but of little use as a source of detailed, statistical information.

W. J. T.

Principles and Practice of Surgical Nursing. By CHARLES D. LOCKWOOD. In collaboration with MILDRED E. NEWTON. 344 pp. $2.75. (*The Macmillan Co., New York, 1932.*)

A reference manual rather than a textbook. The illustrations are many and have been well selected. The writing could be improved upon. In attempting to cover surgical data of interest to the nurse the author has not included a real discussion of surgical nursing as the title would imply.

M. B. D.

Health and Home Nursing. By GEORGE MARGARETTA DOUGLAS. 383 pp. $2.50. (*G. P. Putnam's Sons, N. Y. & London, 1932.*)

Conveys worthwhile information for the lay person. Pictures good.

M. B. D.

Textbook of Pathology. By WILLIAM BOYD. 946 pp. Illust. $10.00. (*Lea & Febiger, Phila., 1932.*)

The book is divided into two parts, "General Pathology" and "Special Pathology." Part I covers briefly such topics as inflammation, tumors and infectious diseases; Part II, the pathology of main organs and organ-systems. On the whole, the information is accurate and is presented in a clear and succinct manner, with emphasis upon the more common diseases.

A few errors (some probably typographical) may be noted: *e.g.*, the concentration of glucose in normal blood is stated to be 1 per cent; 0.1 per cent, is, of course, the truer value. On page 394, "cornification" is employed instead of "carnification." The term "carcinoma simplex" is dangerous, misleading; implies a profounder knowledge of tumors than we actually possess. Caseation is stated to be "partly due to the bacterial toxin, partly to the fact that the tubercle is non-vascular." It is quite unlikely that the latter can be a factor in this process.

Rich's excellent studies in tuberculosis are not even mentioned. Another important omission is Brown's classification of streptococci, according to their reactions on blood-agar plates. There is a contradiction in the discussion of amoebic dysentery. On page 462, it is stated that "The ulcers (of amoebic dysentery) are deeper than in the bacillary form," which is turned about in the table on the next page. The book can be recommended to the beginner in pathology.

W. C.

Life in the Making. By ALAN FRANK GUTTMACHER, with the assistance of Ellery Rand. 1933. 297 pp. $2.75. (*The Viking Press, New York.*)

It is a pleasure to read a book so gracefully informing as the above, and at the same time so void of the common-place claptrap which disfigures most of our popular presentations of sexual subjects. The author's serious intention is maintained throughout by a firm grip upon matter of fact, set off by an omnipresent, critical sense and a strong, dignified, withal engaging literary manner. There is no attempt to be smart, funny, sensational or suggestive, no lapsing into the pretentious vulgarities which the Homeric by-word proclaims plebeian, by comparison with the "godlike coarseness" of the older writers. The only "blurbs" are those common to the paper covers of all recent books. In telling people how they came into the world, Dr. Guttmacher does not mince matters, with regard to the queer blunders sometimes perpetrated by "clumsy old Dame Nature" in her effort to perpetuate species in animals and man. Historic data are mobilized with commendable restraint and the author's critiques of recent scientific theories are pervaded with a vein of sly, dry humor, which is never forced. His adventures before a mirror recall a similar experience of the Viennese physicist, Ernst Mach. Intended primarily for the cultivated laity, the volume conveys much that will be new to those unfamiliar with recent findings in genetics, experimental endocrinology and vitamine chemistry.

F. H. G.

A Text-Book of Neuropathology. By ARTHUR WEIL, M.D. Illust. with 260 engravings. 1933. 335 pp. $5.00. (*Lea & Febiger, Phila.*)

As a review of the present status of neuropathology this volume is quite adequate, covering such topics as congenital malformations, changes through autolysis and fixation and staining methods; with chapters on the more unusual diseases of the nervous system. A bibliography lists recent contributions of importance. Aetiology is briefly discussed, and pathological changes are presented in gross and microscopically, with 260 illustrations. The work would be more stimulating were the obscurities of etiology and the many gaps in our understanding of pathological processes set forth and discussed with more emphasis.

H. J.

Intracranial Tumors. By PERCIVAL BAILEY. 1933. 475 pp. $6.00. (*Chas. C. Thomas, Springfield, Ill.*)

Dr. Bailey describes his book as "a new arrangement of intracranial tumors primarily from the pathological standpoint."

Classification of brain tumors is a difficult subject about which there is much conflict of opinion and Dr. Bailey has gone far to sift the material. Considering the length of the book, one is surprised to find so little pathology and so much of case reporting and anatomy. Pathological discussion would have made the volume more rewarding, if less readable.

F. W. G.

Binocular Vision and the Modern Treatment of Squint. By MARGARET DOBSON. 1933. 107 pp. $2.75. (*Oxford Univ. Press, N. Y.*)

The chief aim of this small volume is to stress the importance of orthopedic training in cases of squint. There are rather sketchy chapters upon binocular vision, binocular balance, suspension of vision and amblyopia. Too much space is given to details about various complicated instruments whose value has not been demonstrated. Such information is available in the catalogues of instrument makers. The book might be rather confusing for the beginner in ophthalmology, and is not exhaustive enough for the experienced practitioner.

B. R.

Blutung and Fluor [Bleeding and Discharge in Gynecology]. By HANS RUNGE. Vol. 9—Medizinische Praxis. 1930. 111 pp. Theodor Steinkopff.

Professor Runge's book, a clear and simple presentation of German lines of thought, is fairly complete but somewhat dogmatic as to causation, diagnosis and treatment of conditions leading to vaginal bleeding and discharge. The physiology of the female genitalia is briefly discussed. Abnormal bleeding is considered under a classification based upon the type of the bleeding. Schröder's teaching as to metropathia hemorrhagica and endometritis is carefully expounded. The second part of the book, dealing with vaginal discharge, stresses the problems of vaginal flora and the chemical protective mechanisms involved.

J. L. M.

Neurological Effects of Syphilis. Diagnosis and Treatment. By BRYAN BUCKLEY SHART. 1933. 92 pp. $2.00. (*Oxford University Press, N. Y.*)

This small book, while containing no new material, summarizes present knowledge of neurosyphilis from the new point of clinical manifestations, prophylaxis and treatment.

H. J.